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NEW PROBLEMS OF APHASIA

BY

KLAUS CONRAD

Homburg-Saar

THE TWO ASPECTS OF APHASIA

BRITISH neurology has never taken the devious paths which mark the past of the doctrine of aphasia in France as well as in Germany. It may have been a sober sense of reality which prevented British neurologists from the beginning from participating in the fantastic speculations which followed Broca's first discovery, relating speech to the base of the third frontal gyrus of the left hemisphere. Mainly, however, it seems to have been the influence of the great British biologists and geneticists, Darwin and Galton, which gave neurological thinking a genetical trend. Under their influence Spencer developed his philosophy, which in turn influenced Hughlings Jackson, whose treatment of the problem of aphasia was diametrically opposed to the theoretical conceptions developed at the same time on the Continent. Whilst on the Continent ideas on the relationship between mind and brain got fixed in a mere rigid scheme, and led to endless and pointless discussions on unprovable things, Jackson had already, towards the end of the last century, succeeded in formulating dynamically the functional mechanism of the nervous system, the far-reaching implications of which, are only fully appreciated now.

The further development of neurological physiology and physiological neurology, carried on by such men as Sherrington, Horsley, and Magnus was set on a straight course by the original impulse. The important contribution by Henry Head on aphasia, dating back to the days after the First World War, showed the considerable difference of outlook between the ideas of British neurology and the Continental conceptions. Thus a straight and uniform development, dynamically functional and genetically oriented, leads from Darwin and Spencer via Jackson and Sherrington to Head and Critchley.

The situation is much more complicated in Continental neurology.

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Side by side with markedly dynamic functional views, one finds rigidly schematic conceptions, showing a strong liking for diagrams, rightly criticized by British neurologists. I do not intend to treat the immense number of theories and opinions which lead from Broca to Pierre Marie and from him via Dejerine to Alajouanine and Ombredane, or from Wernicke via Lichtheim to Kleist, or from Henschen via Niessl von Mayendorf to Isserlin and Lange, or from Arnold Pick to Poetzl, or finally from Wertheimer to Gelb and Goldstein. And amongst all these, alone and little understood, was von Monakow, the first to find the way back to Jackson. The large number of single clinical observations, the majority of which are immediately and prematurely linked with speculations on the localization of the mind in the brain, tend to make one lose one's way. Thus, the problem of aphasia becomes so excessively difficult that von Monakow once said: "There are really few problems, the understanding of which creates such difficulties as aphasia."

The problem of aphasia shows two different faces. One concerns the phenomenon as such; the loss of speech, meaning the reduction of an accomplishment which has been acquired during the life of the individual. Since this is the most differentiated of all accomplishments of the human mind, perhaps an intrinsic part of the mind itself, the endeavour to find the principle by which it could be analysed was bound to lead to almost unsurmountable difficulties. Because again and again, the question arose: What is actually disordered when a human being loses his power of speech? Is it a part of his mind, or is it only a kind of tool which he can no longer use? The almost indivisible relationship between thought and speech was for ever thrown into the discussion. And from the one extreme point of view that thought and speech are one and the same, opinions oscillated back and forth to the other extreme that no relationship whatsoever exists beween the two. The other side of the problem concerns the question of localization in the cortex, in the endeavour to find the law relating loss of speech to a part of the brain. These questions in particular have excited Continental neurology during the last eighty years. The two sides of the problem are, of course, intimately related, but the functional question should take priority over the question of localization. This has often been overlooked, and attempts have been made to solve the question of the localization without knowing at all what is to be localized.

Besides these fundamental difficulties a number of difficulties of a technical nature complicate further the research into aphasia. The phenomenon is such that no animal experimentation can be carried out. Although, particularly nowadays, higher mental phenomena are investigated very successfully in animal experimentation—for example the very

interesting experiments on frustration and artificial neurosis in animals—such experimentation, of course, is not available in the study of aphasia. Even apes, the animals most like man, being naturally aphasic, cannot be made aphasic in order to study the laws of aphasia. A further technical difficulty is the practical non-existence of series of observations with statistical value. We have instead to rely on accidental observations of individual cases, which differ from each other in essential points, so that a real basis for comparison hardly exists. Research on aphasia thus boils down to an industrious collection of odd observations, accidentally found here and there. It often happens, too, that a case studied clinically to its fullest extent is not available for pathological study, whilst in cases which come to autopsy, the clinical studies are insufficient. There are hardly similar examples to be found in other branches of science, where the subject of one's research is so little under personal control. For there will be practically no investigator fortunate enough to observe even two patients, who, being of the same age, suffered the same lesion of the brain, identical in localization and size. A certain change was brought about by the two world wars, during which the number of cases of aphasia, caused by injuries of the brain, was increased immensely. Indeed, the experiences of the First World War led to the first all-embracing presentation of the whole subject of aphasia, in Germany by Kleist and in England by Head. The Second World War, too, brought a sad harvest of brain injuries with it. Thus, new experiences in the field of aphasia could be gained, based on the achievements of the earlier research after the First World War.

My personal experiences, too, are based on material from cases of brain injury, in which I have published numerous papers during the years 1947 to 1950 in various German journals. (Conrad, 1947*a–e*, 1948*a–f*, 1949*a–d*, 1950.)

In the present communication I have divided the subject according to the two sides of the problem just mentioned. The first part is devoted to the phenomenon of aphasia, the question of the nature of the aphasic disorder, based on a thorough analysis of the changed speech of the individual aphasic patient. In the second part I shall deal with the localization of the aphasic disorder, basing my conclusions on the statistical results arrived at from the study of all cases. The question of the nature, i.e. the psychological structure of aphasia, may be dealt with in a few well-analysed individual cases, whilst the question of the relationship between functional disturbances and localization in the brain can only be shown in a statistically pure series of observations.

The Nature of Aphasia

In analysing aphasia, the primary objective is to define and describe the phenomenon, using the terminology of one of the available schools of psychology. The question what is aphasia in psychological terms can be answered in very different ways. There are various possible ways of describing mental phenomena, but each of the descriptive methods is, of course, based on certain theoretical elementary conceptions concerning the mind. Thus, it is possible to define the phenomenon of aphasia by using the terminology of associative psychology, which is also the basis of the so-called classical pathology of the brain. But one could also employ the terminology of Pawlow's teaching on conditioned reflexes, or it could be interpreted as a disturbance of behaviour in the sense of behaviourism. According to the psycho-analytically oriented psychology, one could refer to aphasia as a kind of "slip of the tongue" of the organism. All this would be quite feasible, and by no means wrong, but of questionable usefulness. To me the most promising approach appears to be to describe the phenomenon of aphasia in terms of gestalt psychology. This was done first by Gelb and Goldstein following Wertheimer, Koehler and Koffka, yet without finding many followers, at least, in Germany.

Choosing the basic conceptions of the gestalt psychology for the description and classification of aphasic phenomena, one encountered the difficulty, that it seemed at first that genetic dynamic view-points concerning the evolution and dissolution of the function, as developed by Jackson, could not be applied. For gestalts seemed to be material and finished entities which simply were, and were grasped, or which were not there, and no longer to be grasped. On the other hand the functional genetic ideas, that is, the evolutionary basic conception of Jackson, had to be used in my opinion in the treatment of the aphasic phenomena. This suggested the question, whether what gestalt psychology calls a gestalt does not undergo an evolution too. Cannot one speak of an evolving gestalt? And is there not a close relationship between the disturbances of the formation, the grasping of a gestalt and this evolution of the gestalt (Gestaltwerden)?

Aphasia as a Disorder of Gestalt Formation

Gestalt psychology indeed neglected the question of the evolution of the gestalt at first. A gestalt was always something which simply was there, that struck one in an optical or acoustical pattern. A tune was a gestalt as well as an optical configuration, the picture of a written word or its acoustic counterpart. All these gestalts did not evolve, they were simply there. There are, however, quite simple methods of studying the laws

governing the evolution of the sensory gestalt. If a given constellation of excitation does not reach the threshold which warrants the sensation of a gestalt, the gestalt does not disappear completely, but one has a peculiar sensation of an incomplete, merely implied, gestalt. This is the case, for instance, on diminishing an object to such an extent that the observer can no longer recognize it clearly and without doubt, or on dimming an optical field so much that the light does not suffice to distinguish individual details, or on observing in the lateral field of vision, or, finally, on decreasing the time of exposure in optical perception to such an extent, that during it the figure cannot be grasped. In all these experiments concerning the perception of sub-threshold excitations, the gestalts undergo highly peculiar alterations. They were at first extensively studied by Sander (1926*a–b*, 1928). I cannot enter into details concerning the results he arrived at, but I should like to draw attention to a few essential points he made, inasmuch as they are of importance for the further understanding of aphasic phenomena. Such a figure as, for instance, one composed of bright lines on a dark ground, either strongly diminished, tachistoscopically exposed, viewed in the lateral visual field or extremely dimmed, loses its structure, and thus cannot be reproduced in its exact structure, but gains a sort of physiognomy (Werner). Certain physiognomical qualities dominate the structural qualities. Furthermore, we find that certain parts of the background with which the figure is contrasted appear to belong to the figure itself. Background and figure are no longer differentiated against each other. I call this phenomenon the collectivation of the gestalt. Moreover, such a figure does not seem to be motionless but appears to move, to vary: it shows a certain flickering and wavering life, which is mostly surrounded by a more compact contour. Thus, a compact contour with a flickering core is set up. This tendency to restlessness we call fluctuation. In tachistoscopy this phenomenon results in the fact that on being exposed for the second time, the same figure is seen as totally different from the impression received during the first exposure. A further characteristic is the fact that the figure does not seem to be clear and finished, but that it appears unfinished and incompletely evolved. We speak about the shade of non-finality (Nichtendgültigkeitstönung). In the subject, such an experience gives rise to a feeling of tension, and the tendency to give the figure finality. Then, again, one cannot grasp such a figure at will; one cannot control its structure, but has to accept it as it inflicts itself upon one. One's mode of experience is changed from the critical into the receptive. I call this, the loss of the degrees of freedom. Only when the conditions of excitation have reached such a degree that the figure appears final, structured

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and finished, contrasting clearly and distinctly with its background and ceasing to vary in a fluctuating manner, does this tension slacken. The figure detaches itself, so to speak, as an object from the subject, it is released from a much stronger subject-relationship, faces us coolly and remotely, and only then are we in a position to perceive the figure freely at will. In these experiments we are indeed dealing with the genesis of gestalts.

We refer to all gestalt experiences, in which, owing to incomplete reception of an excitation, the gestalt does not appear as final and finished, as vorgestalt. The characteristics just mentioned are thus characteristics of the vorgestalt. The gestalt psychology has enlarged the conception of the gestalt to fields beyond perception. We encounter the gestalt problem in thinking, in behaviour and in the motor system. Beyond perception it is also much easier to prove the evolution, the actual genesis of the gestalt. One is bound to assume that a creative artist, for instance, conceives at first a kind of bud of the gestalt. The artistic achievement is thus not fully given and structured in the beginning, but seems to be at first a process pregnant with possibilities, without structure but with a strong physiognomy, fluctuating and without definite shape, not clearly detached. The subject is then charged with an impulse to elaborate the process, but without complete freedom, as in front of the finished creation. Only when the work stands fully finished in front of its creator all this has changed, it is fully structured, clearly detached, cool and remote, is experienced with finality and can be perceived at will, with all degrees of freedom. The actual genesis is terminated, the vorgestalt has evolved into the endgestalt.

These phenomena of the actual genesis of the gestalt, are in my belief of major importance in the explanation of the phenomenon of aphasia. This becomes quite apparent, if we try to find the laws governing the development of verbalization out of the psychological stage, which precedes speech in the healthy and normal individual. I have no doubt that here, too, we encounter the process of actual genesis. Exact self-observations show easily that first there is a bud of the gestalt, and that the elaboration of the fully formulated sentence follows closely the laws of actual genesis. This is particularly convincing if the process is slowed down through the use of a foreign language, the speaker's command of which is sufficiently fluent, so that he has not to preformulate the phrase in his native tongue, but thinks it out, so to speak, in the foreign language. One can recognize then, all the experiences of physiognomization, collectivation, fluctuation, shade of non-finality, the tension and the loss of the degree of freedom. Something

similar is experienced when searching for a forgotten word or name. It seems to be on the tip of the tongue, yet it can't be "caught." It would be entirely wrong to describe the sensation as though one were totally at sea, for certain qualities of the whole are given; certain structural indications, as, for instance, a consciousness of the initials, the vowels or the number of syllables. Certain physiognomical qualities may prevail as, for instance, that the name is foreign-sounding, that it is an Italian name and so on. Later verification shows at times that up to then one had not been consciously aware of these physiognomical qualities. One evokes substitutes, knowing immediately that they are not the name one seeks. One is torn by tormenting tension: one cannot give up the search for the name, and one cannot free oneself from it. Only on termination of the process when the name is clearly in front of one, do the characteristics of the vorgestalt disappear. The structure has gained its final gestalt and cannot be elaborated further.

Speech is this verbal gestalting and the understanding of speech a grasping of gestalts. Hence, aphasia can be interpreted as a disturbance of this verbal gestalting, or the grasping of the gestalt, in the sense that the formation gets arrested in a transitional stage. The process of the verbal actual genesis does not lead up to the intended final gestalt, but to errors through the persistence of its vorgestalt. In the case of motor aphasia, it is the motor verbal gestalt which remains vorgestalt, in the case of sensory aphasia the perception of the verbal gestalt remains vorgestalt. According to the concept of Head, I suggest speaking of the loss of the *epicritic* functions of verbalization, that is the *protopathic* "Gestaltwandel der Sprachleistung."

The Process of Verbalization

On examining the actual creative process of verbalization we have to differentiate between two totally different phases. In the first phase we can formulate within ourselves the whole verbal formation, without starting any motor process whatever: the whole verbal contents can be present within ourselves fully formulated before even the slightest movement of tongue or lips is carried out. We start then in the second phase, the highly complicated series of movements which are necessary to formulate any verbal formation. This highly complicated motor tune, or kinetic gestalt, can also be executed without the spoken word making any sense for us; as, for instance, in the case of reading or repeating a foreign language which we do not understand. In the elaboration of the inner language, the first phase, the sense is transformed into inner speech, into verbal gestalt, whilst in the second phase the inner speech is

transformed into a kinetic gestalt. We deal here with two entirely different processes, which apparently are also subject to different disturbances. At times, the first phase of verbalization itself can become arrested midway. If the disturbance is very serious, it may happen that such a patient will fail to reach any internal formulation at all, everything will remain as vorgestalt, which will not pass beyond the stage of vague contours.

In loss of language to such an extreme degree there is sometimes found that peculiar phenomenon of recurring utterances. The totally speechless patient succeeds only in uttering one and the same word or a fragment of a word every time he tries to speak. There can be no doubt that this is not the result of internal formulation. The word is not the result of an actual genesis, but it could rather be compared to the experience of a healthy individual sitting in front of a tachistoscope, which exposes different pictures and shapes, yet for so short a time, that they are perceived all alike as a mere flicker of light. Or, in the case of extreme reduction, any object, whatever its shape, will only appear as a vague bright spot. In the first phase of the making of the vorgestalt, there is always an immense homogenizing of all parts. Of great importance, of course, is the emotional stress which characterizes all the endeavours of such a patient.

If the disturbance is not of such a high degree, a certain level of gestalt is reached. Yet it will remain arrested and bear all the traits of the vorgestalt. What the patient wishes to express will almost always be vaguely recognizable: it is a kind of contour or shape draping a completely diffused core. At times, certain primary structures can be recognized in the form of odd words, fully formulated, but without any syntactical connexion. Emotional stress, fluctuation of the figure, a colouring of non-finality and considerable loss of the degree of freedom characterize the achievement. The smaller the extent of the disturbance the further the process of actual genesis of verbalization goes, and the more it approaches the final gestalt. The least degree of the disturbance exists when the final gestalt can almost be reached, and the patient's power of speech appears to be normal, though lacking ease and fluency, so that he speaks with a noticeable effort.

Quite a different type of motor aphasic disturbance is present, when the first phase, the inner verbalization, can be completed, but the motor formulation, the transposition of the inner word, or phrase, into the necessary motor tunes is not, or is incompletely, achieved. The extremely differentiated kinetic gestalts, which come into existence in order to form the word, can be disturbed to such an extent that not even the least

beginning of a movement can be achieved. This is the condition in so-called pure word-dumbness.

One can see that these are indeed two entirely different mental processes and it is understandable that they can be disturbed quite independently of each other. In fact, the second phase may persist, whilst the first is disturbed. This will show itself in a fairly good ability to repeat, and to pronounce well, words uttered spontaneously. This type of disturbance is the motor aphasia of Broca. On the other hand, the first phase may persist, whilst only the second one is disturbed, in which case one is led to think that this disturbance of speech belongs to the category of apraxic disturbances, as the incapability of purely motor planning is an apraxic disturbance. Mostly, however, both phases will be involved.

The failure to distinguish between these two totally different processes in speech has led to great discussions. And it was mainly the disturbance of the first phase, the inner verbalization, which repeatedly led to aphasias being considered a disturbance of the thinking process. For, indeed, there is a connexion between verbalization and thinking, and when Pierre Marie considers aphasia to be a combination of a disturbance of articulation and one of thinking, he means apparently a combination of these two phases.

Disorders of Receptive Speech

Receptive processes much resemble the expressive side. The understanding of speech, seen from the point of view of gestalt psychology, is a perception of gestalts conveying meaning, quite comparable in the optical field to reading, which demands a perception of script gestalts. In this connexion it has been shown in numerous experiments, that reading is not merely summation of odd letters. This might be the case initially whilst learning to read, but very soon the whole word, and later even the whole sentence, are perceived as gestalts. The grasped gestalt thus becomes more highly structured and differentiated.

The impairment of function in sensory aphasia is such that the patient might be compared to a healthy individual in front of a tachistoscope. He experiences certain sensations of speech which do not reach the level of comprehension. Their formation is arrested midway, and the sensations bear the features of the vorgestalt. Only outlines which surround a diffused core are grasped: the sounds of speech fluctuate; they appear to become extinct too fast for the patient; again and again he asks for a repetition of what has been said. Briefly, he behaves like the individual in front of the tachistoscope. And even if he understands correctly, there remains the element of non-finality, he cannot get rid

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of the feeling that he cannot really understand what he has been told, but is only guessing. He is forced to concentrate, as in an environment the language of which is foreign, and the moment he slackens his concentration he loses all connexion.

Here again we have to differentiate between two totally different phases of achievement. In the first phase, the auditory formation of speech has to be grasped purely auditorily, and to be detached from its auditory background without understanding having necessarily to take place at this stage. The individual must only be capable of detaching the auditory gestalt as such, clearly and sharply defined, final and constant in its whole structure. If he does not succeed in this, we have the phenomenon of pure speech-deafness. The spoken word seems, purely in an auditory sense, not clearly differentiated, fluctuating and non-final. Naturally, comprehension of the meaning suffers in consequence, but it may remain relatively intact. A conversation with such a patient is possible: he impresses one as being slightly deaf, though his hearing may not be impaired. In the second phase, it is necessary to understand the auditory gestalt as conveying meaning. It is here that the step from the gestalt to the meaning has to be taken. Only here we have the understanding of the spoken word, whilst in the first phase one refers preferably still to hearing. Thus if the first phase only is disturbed, the patient is impeded in his hearing, but he might be able to understand whatever he does hear. We are dealing here, with pure deafness for words, frequently combined with a deafness for tunes. If the second phase is disturbed, speech appears to be a senseless noise to the patient, which he at times does not even recognize as speech. This is the true sensory aphasia. Here, too, the disturbance is to be attributed to a retarding of the development of the perception of the sounds of speech, for which the experiments of sub-threshold excitation are very suitable models.

Referring briefly to amnestic aphasia, the impossibility of finding a certain word, I have been able to show here, too, that this disturbance may also be of the same order, in that the actual genesis of certain particularly prominent words, mostly names, remains arrested midway (1949*a*). In severe cases the disturbance extends to all substantives, whilst in others less severe only a few names are affected and not available. In such a disturbance it may be shown particularly well that the same word which is not available at will may be the patient's disposal as part of a whole sentence. This is the well-known case, reported by Gowers, of the patient who could not say "no" on demand, but who finally cried out in despair: "But Doctor, I can't say 'no'!" Gestalt psychology has dealt ex-

tensively with these phenomena, which show that a segment torn out from its context becomes something entirely different, so that under certain circumstances it cannot be recognized at all. The analysis of the disturbances of word-finding showed that also in cases of the unavailability of a name, certain qualities of the name looked for, may be present. The formation is thus also here given as vorgestalt with contours surrounding a core, which remains diffused, physiognomic, fluctuating and non-final, thereby the subject remains receptive, waiting for the wanted name to turn up, but without being able to contribute anything actively.

Summing up what has so far been said, we can conclude that according to the theories of gestalt psychology, aphasia is characterized by a persistent arrest in the course of the highly differentiated processes of the evolution of gestalts. In the expressive part it leads from an inner content of meaning to the formulated gestalt of speech, and from here to the kinetic gestalt, whilst in the receptive part leading from the auditory gestalt of the word to the contents of the meaning. The best model for this is to be found in the experiences of tachistoscopy, in which also the healthy and normal individual may show certain symptoms of alexia. He may grasp, by guessing, certain physiognomies of words, without getting their clear structure, and, though failing to recognize a word, may be able to state something concerning certain qualities of the word's formation. So an alexic patient may physiognomically grasp two words, for instance, yet fail to recognize the word composed of the two. Similarly, he may be unable to spell even one letter out of a correctly read word.

My belief is, therefore, that the true meaning of aphasia, is the failure to develop verbal gestalts to their final gestalts. Thus there is a failure in the development of

(*a*) Verbal gestalts in the process of verbalization out of the preverbal (aphasia of Broca).

(*b*) Verbal kinetic gestalts in the process of motor execution as kinetic motor tunes (pure word-dumbness).

(*c*) Verbal gestalts in the process of perception of the auditory gestalt (pure word-deafness).

(*d*) Verbal gestalts in the process of perception of the content of meaning, out of the auditory gestalts (sensory aphasia).

(*e*) Verbal gestalts in the process of the voluntary evocation of names (amnestic aphasia).

Cerebral Localization and Aphasia

What parts of the brain must be destroyed in order to cause these various kinds of disturbance of speech? Although since the first discoveries

of Broca a large number of observations have been made and reported, ideas and opinions concerning the problem of localization of speech vary extraordinarily. Whilst in certain quarters the first conceptions of Broca, Wernicke and their successors attributing the various processes of speech to quite circumscribed parts of the cortex, are still accepted and adhered to, other authors reject entirely the notion of a centre of speech, assume the existence of a diffuse "field of speech" by no means limited, and tend to regard speech as the function of parts of the brain which are not circumscribed. The vast majority of authors, however, persist in the opinion that the base of the left third, frontal gyrus—the actual motor speech centre of Broca—has to remain intact in order to render motor speech possible. Similarly, the base of the first left temporal gyrus has to remain intact, in order that speech may be understood. These opinions are, as I mentioned previously, based on a vast number of individual observations. An exact statistical examination of the problem has been almost impossible up to now. We are aware, however, of the danger hidden in conclusions arrived at by individual observations only. I have, therefore, statistically interpreted all the observations I have been able to make during the years 1943 to 1945, whilst in charge of a hospital for brain injuries. A total of 808 patients were admitted during this period: 216 of these had shown aphasic disturbances as a result of their injury. Out of these I chose all the cases which had been diagnosed definitely as motor aphasia. The majority of these cases, totalling 96, had fractures of the skull, which had been trephined immediately after injury, penetrating bullet wounds taking the second place. The extent of the damage was then established, so that in almost all cases the approximate extent of the destruction of the grey matter could be arrived at. The centre of the trephined aperture, as shown radiographically, was traced on a chart of the brain and the projection of this centre was then fixed on the surface of the brain. I employed for this purpose a procedure cited by Bay, and also the tables published by Goldstein after the First World War. Fig. 1 shows a general view of the distribution of the centres of these trephine apertures. Cases, which were not simple well-localized fractures, but penetrating bullet wounds were for the time being not entered. Bay has shown the trephine apertures in their projection on the surface of the brain itself. But this can only be done with smaller material than ours, because otherwise too many circles would be projected congruently, blurring the picture. Each of these small circles stands, then, for the centre of a trephine aperture in which the injury has led to motor aphasia. These aphasic disturbances lasted for longer than forty-eight hours, otherwise they would have been entered in a different group of cases, those of transitory aphasia.

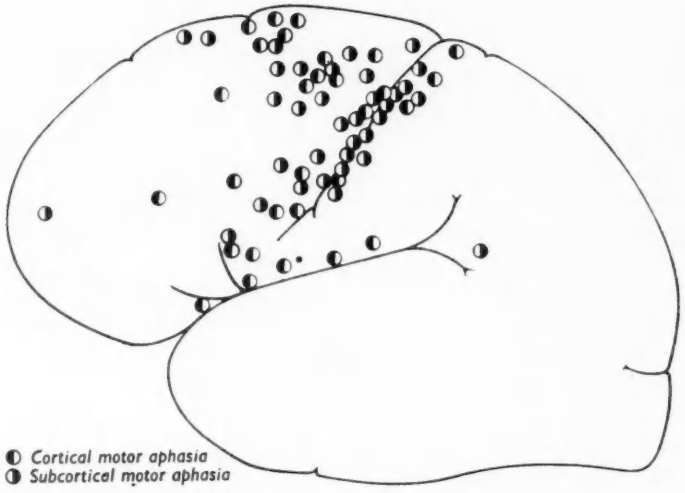

FIG. 1.—General view of all cases of motor aphasia. The circles indicate the middle points of the trephine defects.

FIG. 2.—Cases of "subcortical" motor aphasia (according to the terminology of Wernicke). The figure shows the degree of the speech disturbance immediately after lesion.

The most important result of this series of observations seems to be the fact that practically all foci are situated within the area of the

enlarged motor fields of the cortex. Only a few cases appear exceptions, yet a further study of these shows indeed special circumstances, which makes it probable that they may be neglected. The second, not less important, result shown in this survey is that these foci are not found in increased numbers around the base of the third frontal gyrus. Should this area be the only spot, a lesion of which causes motor aphasia, whether directly or indirectly, the locations of the brain injuries chosen because they caused motor aphasia should show a different distribution: they ought to be concentrically grouped around this spot.

I have distinguished in this figure between the true aphasia of Broca and pure word-dumbness, though I have put all cases showing both disturbances under the heading of motor aphasia. The picture shows that the foci leading to pure word-dumbness are not very different from others: they intermingle. Foci situated in the vicinity of fissura Sylvii, seem to have led only to aphasia of the Broca type.

On eliminating now all the cases of Broca's aphasia and retaining only the cases of pure word-dumbness, that is to say, those cases in which we are mainly dealing with the loss of the second phase of verbalization, a kind of apraxic disturbance of speech, the distribution of the lesions is shown in fig. 2, which also shows the classification according to the severity of the disturbance. Here it seems to be of importance that the foci are grouped around the central fissure. Fig. 3 shows the outcome of the disturbances of speech a few months after the injury. The good results are noticeable. A major disturbance of speech persisted in only one case, whilst very many patients had recovered completely. The remarkable fact to be noted here is that the recovery is the better the further the focus is away from the central fissure. Fig. 4 shows the enlarged motor area of the cortex, according to the excitation experiments of Förster. It is easily recognized that the distribution of foci coincides with this area of the cortex.

In fig. 5 I have recorded all foci which have affected the left hemisphere without an aphasic disturbance being the outcome. One recognizes clearly the blank area around the centre and the base of the motor area of the cortex. Only some odd injuries involve this region. I have examined these cases with particular care because it was of interest to find out why no motor aphasia had appeared. I cannot enter here into the details of each case, and will only mention that in some of the cases the foci were very small, some of the patients were left-handed, and in one case the patient's mind was disturbed for longer than a fortnight, so that an aphasic disturbance could have been overlooked during this period. In another case we had a left-sided hemiplegia without injury of the dura mater, so

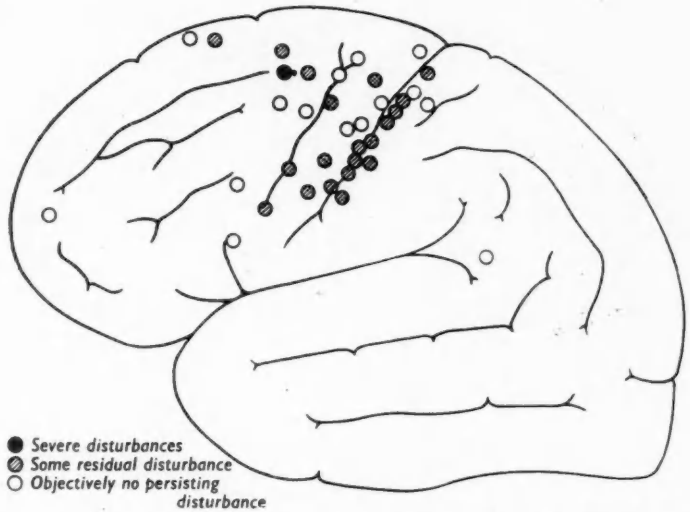

FIG. 3.—The same cases as in fig. 2. showing the outcome of the speech disturbance when the patient left hospital.

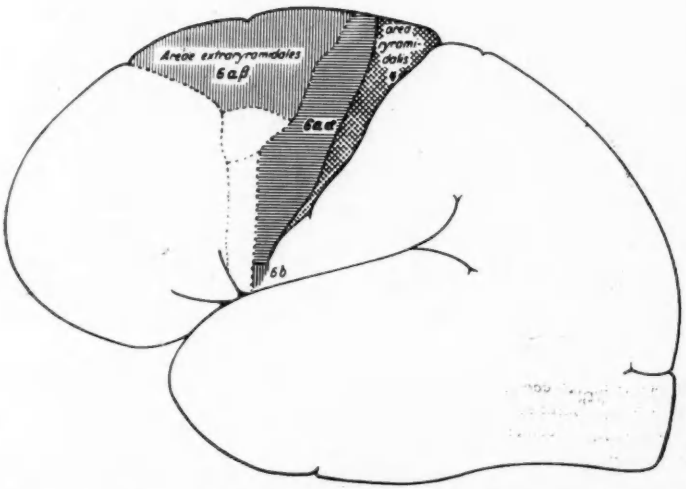

FIG. 4.—The motor region of areas 4 and 6 according to Bradmann (from Förster's Handbuch der Neurolgie, Vol. VI, 4).

that it had to be assumed that we were dealing here with a *contre-coup* lesion only. This check seems to be conclusive inasmuch as it shows

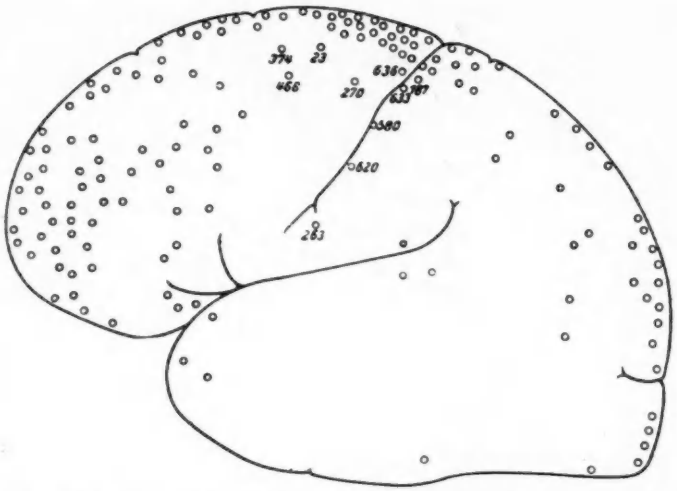

FIG. 5.—The sites of injury of all non-aphasic cases with left-sided lesions in the total material. The few cases, who ought to have aphasia, but had not (numbered), could be explained by exceptional circumstances.

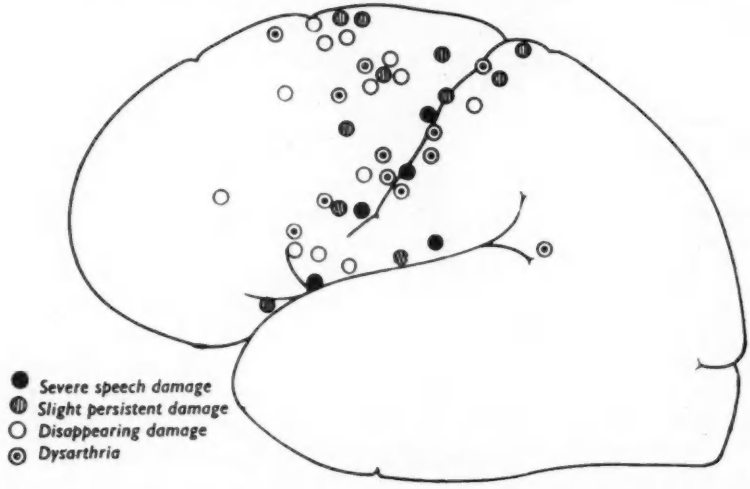

FIG. 6.—The cases of cortical motor aphasia (Broca), shown as ◐ in fig. 1, together with those of subcortical aphasia in which slight troubles of inner verbalization were present. This figure shows the outcome.

indeed that every lesion concerning the motor area of the cortex, be it only severe enough, may lead to a motor aphasia. Within this area, however, a

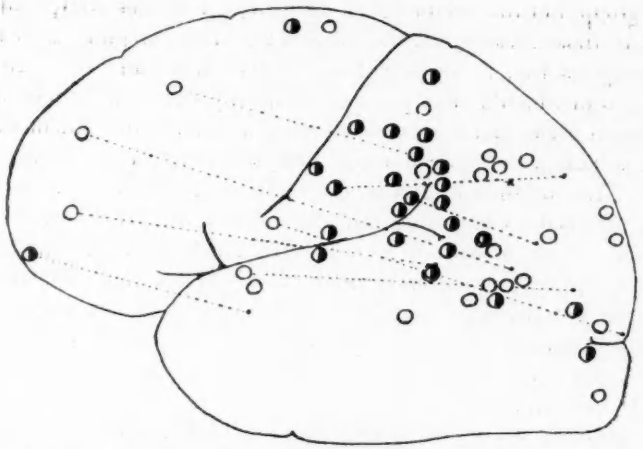

FIG. 7.—The cases with sensory aphasia ◑, practically all of them having troubles in word finding, together with cases of pure amnestic aphasia, shown as O.

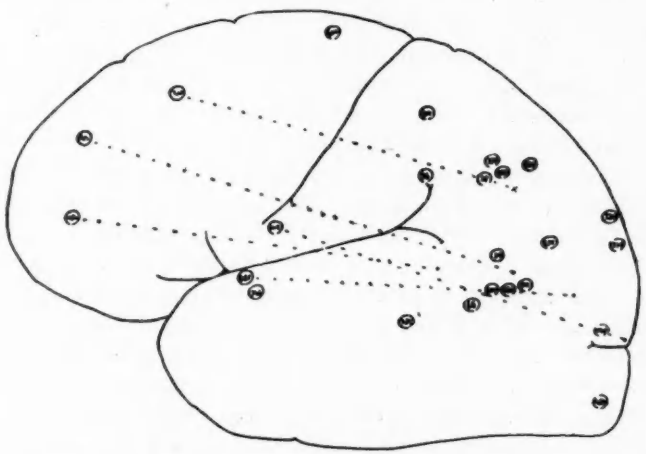

FIG. 8.—All cases of pure amnestic aphasia, without signs of motor or sensory aphasia.

further differentiation is not feasible, except that one has to exclude the upper region near the vertex.

Concentrating now on the cases of Broca's aphasia we see in fig. 6 the cases arranged according to the severity of the residual aphasic disturbance. The lesions causing severe total aphasia are situated in the vicinity of the

central group and the fissura Sylvii. Moreover, a further study had been devoted to those cases where the localization of the trephine area led to the assumption that in all probability Broca's area had been destroyed. In one case in which a large piece of shrapnel penetrated the base of the third frontal gyrus, and was extracted a few days later, the patient showed a motor aphasia, recovering, however, completely after a few weeks. This is equally true for all other similar cases. In none of them had the motor aphasia persisted. Comparing now these cases with those with severe permanent motor aphasia, it is seen immediately that the latter show without exception large areas of destruction. This comparison indicates that not the selective destruction of the base of the third frontal gyrus, but the quantity and size of the destroyed substratum of the brain if the lesion involves parts of the motor region, decides whether or not an irreversible motor aphasia will result.

The question, when does Broca's motor aphasia and when does a pure word-dumbness result, and upon what does it depend that only phase 1 or only phase 2 is absent, has not yet been solved. Pure word-dumbness seems to be often a diaschisis effect comparable to a non-spastic paralysis which can result from a blow on the motor region. If there is no, or practically no, final destruction of brain tissue the disturbance regresses without a motor aphasia of the Broca type becoming apparent. This would be comparable to the speedy regression of a non-spastic paralysis of the arm without a severe spastic phase. The more grey matter has been destroyed the more likely is it that after the cessation of the initial diaschisis effect the spastic stage in the paralysis of the arm, or motor aphasia of the Broca type, i.e. a disturbance of verbalization in the first phase, will occur. According to my belief the two types of motor aphasia do not differ at all in the location of the lesion but solely in respect of such factors as diaschisis and the amount of substance lost.

Those foci which lead to sensory aphasia are crowded in the parietal region and around the base of the first temporal gyrus, as shown in fig. 7. A more exact differentiation between the two phases could not be made here, as it is extremely difficult to arrive at a clear picture concerning the kind of disturbance retrospectively. Recovery was much better in sensory aphasia than in motor aphasia. I think it probable that the proximity of the focus to the primary acoustic field is decisive for the genesis of a sensory aphasia. Fig. 8 shows the distribution of foci in which a purely amnestic aphasia, that is a true impossibility to find a word, was diagnosed. The distribution of the foci over almost the whole brain indicates that here the possibilities of localization are the least. It seems much more as if amnestic aphasia, as a special form of an aphasic disturbance, will result

when the achievement of speech has been impeded through a marginal focus, without motor or sensory aphasia appearing.

In conclusion, I have sought to prove that aphasia regarded as a disturbance of the actual genesis of the process of verbalization is consonant with the basic ideas of Jackson on evolution and dissolution of function. The physiological ideas of Jackson can be transferred to the psychological field. We have then to deal with the evolution and dissolution of gestalts. Aphasia is an example for the dissolution of the process of gestalt in the course of verbalization. This disturbance appears, not through the destruction of special foci in the cortex as presumed by the classical theory, but through the collaboration of various factors out of which only one is the factor of localization, the others being diaschisis and the quantity of the grey matter which has been damaged, which are factors unrelated to localization.

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AGRAPHIA DUE TO A LEFT PARIETAL GLIOMA IN A LEFT-HANDED MAN

BY

O. L. ZANGWILL

Psychological Department, The National Hospital, Queen Square

In a recent paper, Humphrey and Zangwill (1952*b*) reported the case of a left-handed officer who presented an unusual syndrome following right-sided occipito-parietal brain injury. In addition to dysphasia and kindred symptoms ordinarily taken to indicate involvement of the major hemisphere, this patient presented certain signs, most notably massive unilateral spatial neglect, which have not uncommonly been attributed to lesions of the minor hemisphere. It was therefore suggested that the syndrome in this case had a "dual" character, being made up of symptoms ordinarily ascribed to lesions of the major and minor parietal lobes respectively. Although doubt has been cast on this interpretation (Critchley, 1953), not without good reason, it may be argued that the concept of "dualism" in parietal lobe symptomatology is of sufficient interest to justify further inquiry.

A feature of particular interest in the Humphrey-Zangwill case was *the absence of significant agraphia.* Although the patient's writing showed some derangement in the first month after injury, no defects of letter-formation or spelling were in evidence at any stage. Further, the writing defect recovered completely despite appreciable residual disability in other aspects of language. It was therefore felt that the early disturbance of writing warranted treatment, not as a primary agraphia, but as an expression of the syntactical defect of speech. This lack of true agraphia was brought into relation with the fact that the patient, although left-handed, had always written with the right hand and it was tentatively suggested that the cerebral mechanisms governing writing had become built up in the left hemisphere. Although the relations between preferred writing-hand, laterality of lesion and agraphia are far from clear (Herrmann and Poetzl, 1926; Humphrey and Zangwill, 1952*a*), it may be argued that the hypothesis put forward on the basis of this case merits closer examination. In particular, the presence or absence of agraphia in sinistrals

who have sustained comparable lesions of the left hemisphere should evidently be ascertained. One such case will be reported in the present paper.

Case Report

The patient was a clerk, aged 42, who regarded himself as *naturally left-handed though he had always written with the right hand.* He thought that he had wanted to write left-handed but had been prevented at school from doing so. He was consistently sinistral for skilled unimanual tasks (use of knife or toothbrush, throwing, dealing cards) but batted and held a rifle right-handed. He was left-footed but right eye-dominant. He knew of no left-handedness in his family.

Case No. 19803: The patient was admitted with complaints of irritability and depression for the past two years together with headaches and difficulty in concentration in the two months preceding admission.

Two months previously, he had a severe headache of sudden onset which persisted for two days and which was associated with some degree of mental confusion. On the following day the patient awoke apparently well and returned to work, but found great difficulty in the conduct of an important business interview. He found it impossible to formulate any coherent remark or adequately follow the course of the conversation. At the same time, he noticed that he was unable to read properly, words and letters appearing as a jumble. These symptoms improved over the next few days but the patient remained unable to cope with matters of office routine ordinarily well within his competence. His comprehension of speech remained mildly defective and he had some difficulty in reading. He also noticed that his hand-writing had altered, becoming more rounded, and that he occasionally mis-spelled words and introduced words which he had not meant to write. Over the next few weeks, the patient complained of intermittent severe headaches, associated with nausea and later with vomiting, and of rushing noises in the head, which were not, however, continuously present.

On *neurological examination,* the patient gave no definite evidence of verbal dysphasia and was able to perform complicated tasks to order without mistake. When giving his history, on the other hand, he appeared to have difficulty at times in understanding all that was said to him and in finding appropriate words. The patient was well orientated in all spheres and his emotional reactions appeared adequate.

The principal neurological findings were as follows: V.A.R. 6/9, J 10; V.A.L. 6/9, J 2. Mild bilateral papillœdema. Right homonymous hemianopia to confrontation. Slight and variable hypoæsthesia in upper face, most marked to pin-prick, and early right facial weakness most marked on emotional expression. Power slightly reduced for movements in the proximal parts of the right upper limb, the lower limbs being more slightly and diffusely affected. No defect of tone or co-ordination. Tendon reflexes brisker on right apart from ankle-jerk. Abdominals present and right plantar ? extensor. Sensory findings comprised a mild impairment of light touch and variable attention defect to pin-prick in right limbs, impaired position sense in right fingers and toes and reduced vibration sense at right ankle. Temperature sensation normal throughout. Slight reduction in two-point sensibility and graphæsthesia in the right hand.

The patient presented no definite dyspraxia but was a little slow and awkward in miming actions and in manipulations involving the two hands. No finger

agnosia and no left-right disorientation on his own body though definite confusion of left and right on the examiner. No dressing dyspraxia could be elicited but the patient admitted to some difficulty in putting on his clothes in the month prior to admission. No apparent tendency to neglect the right side of his body or the right half of extra-personal visual space.

Visual fields.—Perimetry revealed an incomplete right homonymous hemianopia, extending to 35 degrees from the fixation point. Screen-testing with a 4 mm. white object showed a field defect extending to 10 degrees from the fixation point, slightly more marked in the right lower quadrants.

Electroencephalography.—The right side was relatively normal. On the left, there was continuous slow activity at about 4 c/sec. in the frontal region and around 1 c/sec. of moderate to low amplitude in the anterior and mid-temporal region.

Ventriculography.—On ventricular puncture an air-filled cyst was encountered in the left parietal region. The ventricular system was markedly displaced to the right, the septum pellucidum being displaced approximately 2 cm. anteriorly. There were also pressure changes in the posterior parts of the ventricular system, corresponding with the position of the cyst.

Arteriography suggested the presence of a rapidly growing glioma in the posterior parietal region, verified by a left parietal aspiration biopsy.

Psychological examinations.—The patient was repeatedly examined in the Psychological Department over a three weeks' period, during which time his mental condition underwent no significant change. Apart from some fluctuation in attention level, co-operation on testing was well sustained throughout.

(1) *Speech*: Expressive speech was very little impaired. The patient made no mistakes over common names but there was occasional hesitation over an unusual name. Serial speech was intact. Verbal fluency as assessed on speed tests was significantly depressed. No paraphasia.

(2) *Comprehension*: Although no unequivocal defect in comprehension could be demonstrated, the patient's conversation suggested a minimal impairment in understanding of speech.

(3) *Reading*: Reading of individual letters, words and digits was accurate and continuous reading contained only a few paralexic errors. Yet general comprehension and recall of material read was undoubtedly defective. When asked whether he could read the newspaper, the patient replied: "I don't assimilate it. I don't get beyond the headlines and then I forget."

(4) *Writing*: The patient could write his name on request but *spontaneous writing was virtually impossible.* Attempts to write a letter were marked by constant false starts and erasures and seldom proceded beyond the first line or two. There were outspoken malformations and substitution of letters, though never of whole words. In writing the alphabet (which the patient could recite without error) about one-quarter of the letters were malformed, omitted or transposed but the particular letters affected varied on different occasions. On the other hand, numerals from 1 to 20 were always written correctly and in proper sequence. In writing to *dictation*, errors multiplied rapidly and the outcome was often illegible.

It was found that the patient could *copy* words and letters with normal speed and accuracy and could easily read what he had written. *Oral spelling* was but little affected, the patient making only one mistake at the 12-year age-level on a standard scholastic test. The same words could not, however, be taken down to dictation without numerous errors in letter-formation and spelling.

In view of the patient's *mixed hand-preferences*, a number of special dictation tests were given in which he was required to take down a standard word list first with the right (preferred writing) hand and then with the left. The results of one such test are shown in fig. 1. It will be seen first, that the quality of the left-

FIG. 1.—Dictation Test. Total letters: 63. Number of correct letters: right hand, 50; left hand, 45. Mean writing time per word: right hand, 25·3 sec.; left hand, 18·4 sec.

handed script is little, if at all, inferior to that of the right-handed script; and secondly, that the incidence of letter-substitutions is much the same whichever hand was used.

(5) *Calculation*: Although basic arithmetical concepts and procedures were understood the patient could do none but the very simplest sums on paper or in his head. Money sums (e.g. 2s. 6d. — 8d.) were quite beyond him. He could

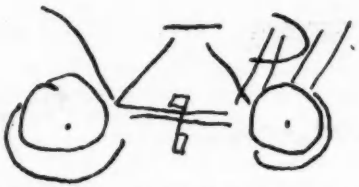

FIG. 2.—Bicycle drawn from memory.

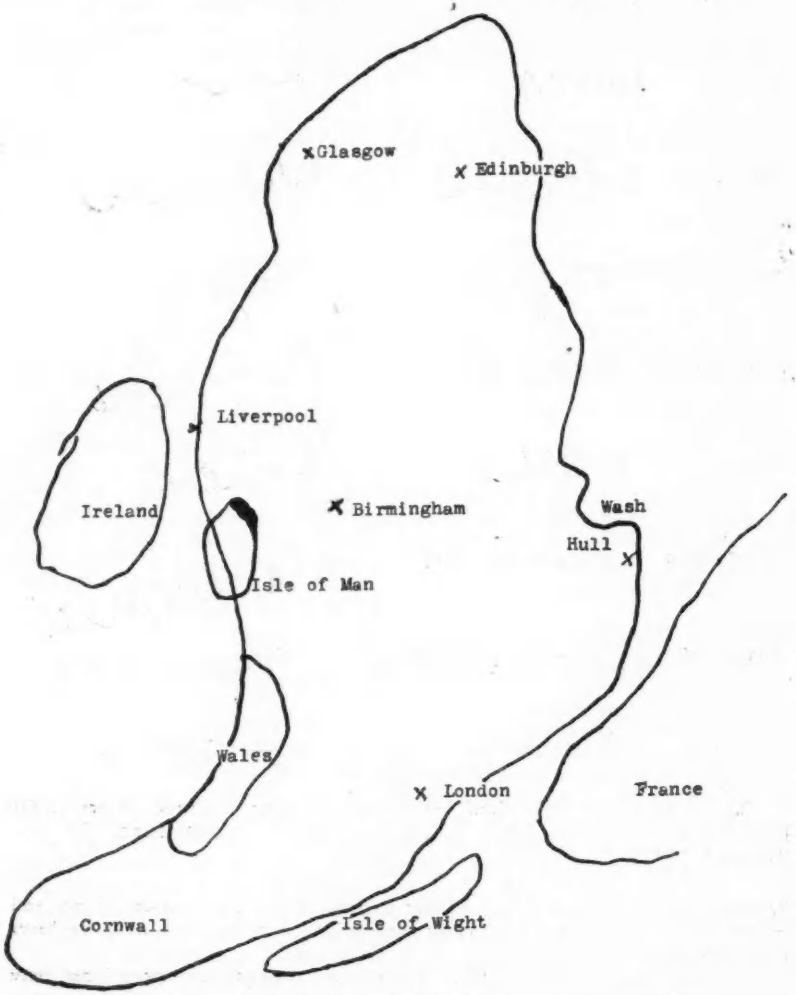

FIG. 3.—Map of England drawn from memory.

repeat the multiplication tables by rote but was unable to apply them to particular instances.

(6) *Copying and drawing*: Simple geometrical designs (square, circle) were copied easily but more complex figures (cube, swastika) gave great difficulty and were seldom completed. A bicycle was drawn very inadequately, and with some disconnexion of parts (fig. 2). A map of England was drawn crudely but without neglect of either side and with approximately correct location of some principal towns (fig. 3). The Stanford-Binet "Memory for Designs" subtest was executed adequately after three exposures of the test figures and there was no evidence that the right-hand side of the drawing gave greater difficulty than the left.

(7) *Assembly and construction*: The patient could readily copy simple and regular match-stick designs but failed if the models were irregular or complex. On Kohs Block-Design tests, only the simpler models could be correctly assembled. There was no tendency to neglect the right-hand side of any of these designs. The patient was unable to cut a four-pointed star out of paper with scissors unless the outline was first drawn by the examiner. Nor could he solve either part of the Stanford-Binet "Paper-Cutting" subtest.

(8) *Visual perception*: Pictures were described and interpreted in normal fashion and the patient attained a score on the Wechsler-Bellevue Picture-Completion subtest significantly above the mean for his age-group. He was able to count scattered objects (beads) without difficulty, and in this task proceeded consistently from left to right and did not neglect items on his right-hand side. There was no disturbance of depth or distance perception and no evidence of colour-agnosia.

(9) *Spatial orientation*: The patient denied ever having lost his bearings in familiar surroundings or having failed to recognize a familiar building. He showed no obvious loss of topographical memory and did not lose himself while in hospital.

(10) *Intelligence*: On the Wechsler-Bellevue Vocabulary test, the patient scored 31, placing his pre-morbid IQ in the region of 120. On the Wechsler-Bellevue Full Scale, his IQ was 85. Performance on the Weigl Sorting Test was variable but probably impaired.

In summary, this is a case of dysphasia and kindred disorders of language resulting from a left-sided parietal lobe neoplasm in a left-handed man. The dysphasia was relatively mild at the time of our examination and predominantly receptive and semantic in character. On the other hand, the patient presented a severe dysgraphia, marked by constant literal errors, which occurred irrespective of which hand was employed in writing. Further, although there was no definite dyspraxia, marked constructional anomalies and some degree of right-left disorientation were clearly in evidence. There was no finger-agnosia, right-sided sensory, motor or visual neglect, or disorder of spatial orientation. Intellectual level was high-grade without appreciable general deterioration or personality change.

Discussion

The first point to be ascertained is the precise nature of the patient's *handedness*. As Critchley (1935) has rightly pointed out, too much credence cannot be paid to descriptive studies of cerebral disorder in sinistrals until more data are afforded as to the nature of manual preference.

Although the evidence in the present case (particularly as regards familial antecedents) is less complete than one might wish, by far the most probable interpretation is that the patient was a true sinistral whose manual preferences had been complicated by early conversion to right-handed writing. As Humphrey (1951) has shown, such conversion is liable to influence later manual habits not only in regard to writing itself but also in promoting a greater tendency towards ambidexterity. In the present case, the facility shown by the patient in writing with either hand, together with his some what mixed peripheral preferences, render it virtually certain that he fell into the category of "shifted sinistrals" as defined by Russell Brain (1945).

The pattern of manual preferences in this case is virtually identical with that described by Humphrey and Zangwill in their earlier case report. Their patient was likewise a right-handed writer who consistently preferred his left hand for all other skilled unimanual acts and played all games left-handed. In view of the fact that the lesion in both cases was posterior parietal—right-sided in the earlier case and left-sided in the case under discussion—the resultant syndromes would appear worthy of careful comparison.

The principal clinical findings in the two cases are summarized in Table I. If we consider first the *disorders of language,* it will be seen that some dysphasia, predominantly receptive and semantic, was present in both cases but that in neither was it severe at the time of our examination. Reading was mildly, and calculation severely, affected in both patients. In the case of *writing,* on the other hand, the picture in the two cases is entirely different. In Humphrey and Zangwill's patient, writing was but little affected and the mild syntactical derangement shown on early examination fully recovered within a month after injury. In the present patient, however, it is not too much to say that *agraphia was the main presenting symptom.* As we have seen, the disorder in writing was literal in type, being marked by numerous malformations and substitutions which the patient was powerless to correct. In view of the fact that his oral spelling was little, if at all, affected, these errors cannot be attributed to dysphasia. Further, the fact that the patient could copy script and reproduce designs at least as complex as letters of the alphabet would appear to preclude an explanation of the agraphia in terms of a general constructional disability. In short, the writing disturbance corresponds essentially to what Goldstein (1948) has termed *amnesic-dyspraxic agraphia* and which appears to derive from a primary weakness in the recall of letter-outlines and in the execution of serial graphic forms.

If we compare the symptoms presented by the two cases in the spheres of *gnosis and praxis,* it will be seen that visual agnosia was absent in both

TABLE I

	Humphrey and Zangwill's (1952a) case	Present Case
Age	31	42
Handedness	Left, apart from writing	Left, apart from writing
Lesion	Right occipito-parietal brain injury	Left parietal glioma
Intellectual level	Superior	Above average
	Neurological Signs	
Motor functions	Early left hemiparesis, very little residual disability	Slight reduction of power in right upper limbs
Sensory functions	Gross left-sided sensory loss at first; some persistent disability	Some impairment of touch and position sense in right limbs
Visual fields	Early left inferior quadrantic field defect; recovered	Right incomplete homonymous field defect
	Language Functions	
Speech	Early dysphasia, mainly nominal and semantic; very mild residual disability	Mild dysphasia, mainly receptive and semantic
Reading	Slow at first, with some defect of comprehension	Early episode of alexia; largely recovered but with persistent impairment of comprehension and retention of material read
Writing	Early disturbances of grammar and syntax, recovered within one month. No defects of letter-formation	*Gross defects in letter-formation, and in writing words to dictation*
Spelling	Intact	Very slightly impaired
Calculation	Moderate impairment; some residual disability	Markedly impaired
	Gnosis and Praxis	
Visual object agnosia	None	None
Colour agnosia	None	None
Unilateral visual neglect	*Present and persistent*	Absent
Dressing dyspraxia	Present at first	Reported present, not witnessed
Motor dyspraxia	Presumed left-sided motor dyspraxia at first	Doubtful mild bilateral ideo-motor dyspraxia
Right-Left disorientation	Present on examiner	Present on examiner
Finger agnosia	Absent	Absent
Loss of topographical orientation	*Some at first*	Probably none
	General Intellectual Level	
Abstraction	Impaired at first	Slightly impaired
Attention	Sustained with difficulty at first; no permanent impairment	Some difficulty in concentration
Memory	Mild early impairment	Probable slight impairment
	Personality Changes.	
Mood	At first mildly euphoric; no permanent personality change	Some increase in irritability and loss of drive

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patients and in neither was there outspoken or persistent motor dyspraxia. In Humphrey and Zangwill's case, however, symptoms of *unilateral neglect* were very pronounced, being still in evidence in the visual sphere six years after injury. This symptom could not be ascertained in the present case despite careful and repeated examination. Further, more pronounced defects of right-left orientation and topographical sense were present in the earlier case. Visual-constructive disabilities were present in both cases and will be further considered below. In neither patient was there any gross intellectual loss and personality changes were minimal.

We may now consider the implications of these findings in relation, first, to the question of handedness and cerebral dominance; and secondly, to the concept of "dualism" in lesions of the parietal lobes in sinistrals. As regards *cerebral dominance,* it will be borne in mind that, in Humphrey and Zangwill's case, the right hemisphere appeared to be dominant in regard to language functions. It was suggested, however, that the absence of significant agraphia might perhaps be attributed to selective transfer of dominance for skill in writing to the left side in consequence of early conversion to the use of the right hand. The incidence of agraphia in the present case (a left-sided lesion in a right-handed writer) might be held to lend support to this interpretation. At the same time, there are serious objections to the view that the cerebral mechanisms governing writing are necessarily located in the hemisphere contralateral to the preferred writing-hand. In the first place, agraphia has sometimes been reported in both right-handed and left-handed patients who have sustained lesions of the hemisphere *ipsilateral* to the preferred writing-hand (Herrmann and Poetzl, 1926; Marinesco *et al.*, 1938; Humphrey and Zangwill, 1952*a*, Case 5). In the second place, there may occasionally be no agraphia in cases with appropriately situated lesions of the hemisphere contralateral to the preferred writing hand (e.g. Humphrey and Zangwill, 1952*a*, Case 4). And in the third place, the evidence regarding the effects on cerebral organization in general of training in the use of the non-preferred hand for writing is decidedly equivocal (cf. Needles, 1942). It may be concluded, therefore, that Humphrey and Zangwill's attempt to relate absence of agraphia to enforced handedness change in their case was almost certainly an oversimplification. Whatever may be the ultimate implications of such a change for the transfer of dominance, it is extremely likely that the agraphia in the present case is an expression of general left hemisphere dominance for all language functions.

We may now consider briefly the relevance of this case to the concept of "*dualism*" in parietal lobe symptomatology advanced by Humphrey and Zangwill in their earlier study. As Critchley (1953) rightly points

out, this conception implies the acceptance of certain symptoms as specific to lesions of the minor hemisphere—an assumption which has failed to secure general acceptance. It may, however, be pointed out that the principal feature adduced by Humphrey and Zangwill as indicative of "minor" parietal lobe involvement, viz. massive neglect of the contralateral half of extra-personal space, could not be established in the present case and, despite the recent observation of Denny-Brown and Banker (1954), is extremely rare in cases with lesions of the major parietal lobe.

It is of course true that constructional and dressing disabilities are not infrequent with parietal lesions of either hemisphere. None the less, there is some evidence that the pattern of disability depends in some measure at least on the laterality of the lesion (McFie, Piercy and Zangwill, 1950; Hécaen, David, van Reeth and Clément, 1953). In the present case, the performance of the patient on a variety of constructional tests showed certain features more suggestive (in our experience at least) of major rather than of minor hemisphere involvement. In the first place, there was a genuinely dyspraxic element, altogether parallel to the concomitant defect in letter-forming, and typically lacking in the performance of patients with right-sided parietal lesions, including the ambidextrous patient described by Humphrey and Zangwill (1952*b*). Such patients tend to fail on constructional tasks not because they cannot manipulate the component elements but because they lack discriminative visual judgment. In the second place, there was a suggestion of an amnesic element in the recall of visual patterns (including letters of the alphabet) seldom seen in cases of right parietal lesion. Although the evidence is far from conclusive, it may be suggested that the constructional disabilities in this case were due not to spatial agnosia, as in cases of right parietal lesion, but to *an amnesic-constructive dyspraxia altogether parallel to the amnesic-dyspraxic agraphia.* Further, in view of the fact that both these symptoms can be confidently ascribed to a lesion of the major hemisphere, and that no unilateral neglect in any sphere could be ascertained, it is unnecessary to postulate a "dual" symptomatology in this case.

In conclusion, it may be said that the balance of evidence in this case strongly suggests that the left hemisphere, despite the patient's left-handedness, was almost certainly dominant with regard to all language functions. Whether this left dominance is due to "stockbrainedness" in the sense of Foster Kennedy (1916), to acquired preference for the right hand in writing, as suggested by Tilney (1936) in explanation of his own aphasia, or to some combination of innate and acquired factors, as originally proposed by Bramwell (1899), cannot be discussed here. Further, the possibility of bilateral representation of language in sinistrals, adduced by several recent

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authors (Chesher, 1936; Conrad, 1949; Subirana, 1952) cannot be wholly excluded, even if such an assumption might appear *prima facie* improbable. Whatever the factors responsible for dominance may be, this case provides yet another illustration of the fact that aphasia resulting from left-sided lesions in left-handed patients is far from exceptional.

SUMMARY

(1) A case complementary to that reported by Humphrey and Zangwill (1952*b*) is described. The patient, who was left-handed apart from writing, developed mild dysphasia and severe agraphia from a glioma involving the posterior parietal region of the left hemisphere.

(2) The clinical findings in the two cases are compared and their relevance to the problem of cerebral dominance in sinistrals briefly assessed.

I am deeply indebted to Sir Charles Symonds for his kindness in permitting me to study and communicate this case. I have also to thank Dr. J. McFie for his assistance in psychological testing, and Dr. R. T. C. Pratt for his helpful comments on this paper.

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LANGUAGE LATERALITY IN LEFT-HANDED APHASICS

BY

HAROLD GOODGLASS AND
F. A. QUADFASEL

(From the Aphasia Unit of the Neurological Section, Neuro-Psychiatric Service, Boston Veterans' Administration Hospital)

DEFINITION, HISTORY AND PROBLEM

LATERALITY refers to the relationship of a cerebral function, or the symptom of its disturbance, to one cerebral hemisphere. Although the term is used mostly in connexion with handedness, aphasias, and agnosias, it has much wider implications and, in its broader sense, it constitutes the basis for localizing the lesion in cerebral hemiplegia in the opposite hemisphere.

The association of right hemiplegia and speech disturbance can be found in the description of aphasia by Goethe (1796) and others. The idea of localization of speech in the left hemisphere was first conceived by Marc Dax in 1811 and presented at a lecture in 1836, but was not published until 1865 (Broca, 1865). It was reiterated by his son, Gustave Dax, in 1863 (Souques, 1928). When Broca, too, concluded that the posterior part of the third frontal convolution, especially on the left, was essential for intactness of the faculty of speech (1861–1864), he offered no explanation for this lateralization, nor suggested any significance in terms of handedness or cerebral dominance (Broca, 1863*a*, *b*).

The idea of the linkage of handedness and speech was first formulated by Bouillaud in April 1865, when he spoke of "gaucherie cerebrale," again by Baillarger in May 1865, and Broca in June 1865 (*See* Broca, 1865; Souques, 1928; Riese, 1947). In 1874 Jackson spoke of the "leading hemisphere" and of the localization of both propositional and emotional speech in the left hemisphere, and of emotional speech alone in the right hemisphere. Jackson (1880), and Ogle (1871) contributed some cases of left-handed individuals who had been rendered aphasic by right cerebral lesions. In 1877 Kussmaul stated that innervation centres are bilateral for all manual work but most people are right-handed and train the left hemisphere for most skills. "On this fact and the preponderance of aphasic disturbances in lesions of the left hemisphere rests the hypothesis that most people are 'left-brained speakers'."

From such facts and opinions the inference was made that there is cerebral dominance as a property of one hemisphere. The dominant hemisphere now was assumed to control the preferred hand, often the preferred eye and foot, and, if damaged, to produce aphasia. Handedness was now used as evidence of dominance of the hemisphere opposite to the preferred hand (e.g. Weisenburg and McBride, 1935, p. 435).

While Kussmaul does not speak of the influence of handedness on speech or its use for treatment, others like Brown-Séquard, (1874), suggested that by development of the movements of the two sides of the body the two sides of the brain might be developed as regards the mental functions. Buzzard (1882) more specifically believed that the use of the left hand would develop the corresponding convolution in the right cerebral hemisphere. "The idea is, as I have said, in the failure from diseases of Broca's convolution, to develop by afferent impulses the corresponding convolution in the right cerebral hemisphere. With the same view, I make the patient go through gymnastic exercises with the left arm and delicate movements with the fingers of the left hand, with the aim of producing that *dexterity* (using the term in its etymological sense) with which the faculty of expression by speech and signs is so intimately associated" (p. 439).

Similar ideas have continued to limit the thinking of neurologists to the present day. They are implicit in the following two explanations offered for "crossed aphasia," or aphasia caused by a cerebral lesion on the same side as the preferred hand. When a left-handed person becomes aphasic as a result of a left cerebral lesion, the circumstances of his having learned to write with his right hand is generally credited with conferring dominance to the left hemisphere (cases of Bramwell, 1899, Chesher, 1936). When a right-handed person becomes aphasic as a result of a right cerebral lesion, one explanation offered is that he was congenitally left-handed and right-brained (from left-handed stock) but learned to prefer the right hand as a result of environmental pressure.

These two theories contradict each other. The first holds that the training of a hand for writing can transfer the dominance for speech to the hemisphere opposite the hand used. The second theory holds that dominance for language persists in spite of the pre-eminence of the ipsilateral hand in all activities.

The occurrence of aphasia with left hemisphere lesions in the great majority of patients, most of whom are right-handed, is undisputed. However, the assumption that this constitutes a dominance of the left hemisphere, and that conversely left-handedness is necessarily linked with a dominance of the right hemisphere in language, requires further study.

Evidence contradicting this traditional view has accumulated rapidly in the last five years. It has even led some investigators (Wepman, 1951, and Milner, 1952), to hold that right hemisphere language representation is extremely rare or non-existent. It has led Girard (1952) to define handedness in terms of language laterality: "Le gaucher n'est pas celui qui écrit avec la main gauche mais celui qui parle avec le cerveau droit."

Data on Laterality in Left-handed Patients

One method of investigating this question would be to examine a large number of cases of left-handed individuals with lesions of the language area. Individual series of such character are so small as to have little statistical significance. In our own two consecutive series totalling 320 cases examined for aphasia, 13 cases of left-handedness with unilateral lesions of the anatomical language area were found. The first series consisted of 76 aphasics found during a post-traumatic epilepsy study at Cushing General Hospital, in which all (246) cases were also examined for aphasia and handedness. Out of these, 7 were found to be left-handed and have a unilateral lesion only. In the second series of 244 consecutive cases examined in the Aphasia Unit at Cushing Veterans' Administration Hospital, and now at the Boston Veterans' Administration Hospital, 6 such cases were found. In addition, we have searched the neurological literature for cases of this type and have been able to compile a series of 110 additional cases.

The criterion of left-handedness used in this paper is that the individual performs most skilled acts (eating, cutting, handling tools) with the left hand and considers himself left-handed. Writing with the right hand by an otherwise left-handed person does not constitute ambidexterity. No cases were included in which left-handedness was known to be the result of an early left cerebral injury. It is recognized that this criterion lumps together individuals of every degree of left-handedness. It would be desirable to investigate the strength of left-handed preference in relation to language laterality if it were possible to obtain a satisfactory inventory of the manual skills of each aphasic patient. Bethe (1933), however, believes that even such determination in adults would be inadequate as an indication of native tendency to handedness. Chesher (1936) suggests that writing with the preferred hand is necessary for pure left- or right-handedness, and that "pure" handedness is always correlated with exclusively contralateral language laterality. However, the cases of Mendel (1912), of Weisenburg and McBride (1935), and of Ballantine and White (1953), contradict this rule. Moreover, the few case reports which mention the writing hand indicate that the vast majority

of left-handers were taught to write with the right hand. Thus, left-handed writing cannot be used as a definite criterion for predicting language laterality.

Another possible basis for classifying left-handers (Bramwell, 1899; Kennedy, 1916) is the presence of left-handedness in the family background. There is little or no evidence that the strength of the individual tendency to left-handed preference is determined by the amount of left-handedness in the family, and it is impossible to evaluate the strength of familial influence unless all of the patient's antecedents are left- or right-handed.

Out of the total of 123 left-handed cases, 50 patients showed aphasia in connection with right hemisphere lesions, and 8 showed absence of aphasia in spite of seemingly adequate left hemisphere lesions. All 58 were apparently right-brained for speech. Sixty-five patients who were apparently left-brained for speech were made up of 53 who showed aphasia with left hemisphere lesions (crossed aphasia), and 12 who showed absence of aphasia with right hemisphere lesions. This proportion is not necessarily an accurate representation of the entire population of left-handed aphasics because on one hand the cases were published as examples of crossed aphasia, and on the other hand as illustrations of the classical theory of dominance. If anything, the prejudice is in favour of the latter. It is certainly to be expected that a history of left-handedness has gone unnoticed in many apparently ordinary cases of right hemiplegia and aphasia, and which are therefore unreported. If we take only those sources which claim to offer an impartial tabulation of consecutive left-handed cases with aphasia from their own experience (Weisenburg and McBride, 1935; Chesher, 1936; Conrad, 1949; Humphrey and Zangwill, 1952*a*; Roberts, 1951; Wepman, 1951, and the present report), the proportion is 43 to 23 in favour of left-handedness and left cerebral lesions. The total figures, as summarized in Table 1, indicate that 53 per cent of the patients fail to show the expected relationship of left-handedness with right-brainedness for language.[1] The addition of the negative cases (those in which laterality is inferred from the absence of aphasia in a lesion of the supposed language area), does not change the proportion significantly.

[1] The foregoing figures do not include 27 cases of speech disturbances in left-handers and ambidexters with right-sided brain injuries reported by Ludwig, who, in 1939, in 979 German World War I soldiers with right brain lesions, found that 27 of 99 left-handers and ambidexters in this group had aphasia. As Ludwig was primarily concerned with the right-handers, he combined his figures for left-handers and ambidexters, did not mention his criterion of ambidexterity, the types of lesions involved or any other individual case data.

TABLE I.—INCIDENCE OF APHASIA IN LEFT-HANDERS FOLLOWING UNILATERAL LESIONS OF THE ANATOMICAL LANGUAGE AREAS

All left-handers seen or reported	*Language area apparently on left 65 cases (53%)*		*Language area apparently on right 58 cases (47%)*		*Total: 123 (100%)*
	Lesion on left with aphasia	*Lesion on right without aphasia*	*Lesion on right with aphasia*	*Lesion on left without aphasia*	
Writing hand:					
Right ...	17	3	14	1	35
Left ...	4	1	9	1	15
Not given ...	32	8	27	6	73
All cases ...	53	12	50	8	123

From these data two conclusions are inevitable:

First: The tendency for aphasia to follow brain lesions contralateral to the preferred hand is much greater in right-handed than it is in left-handed individuals.

Second: The frequency of left hemisphere lesions with aphasia is greater than the frequency of right-handedness, in fact, about one-half of left-handed individuals with aphasia have a left hemisphere lesion.

In the authors' opinion, these data are most consistent with the hypothesis that the various functions, e.g., language, handedness, eyedness, establish themselves independently more on one side or the other, but most often on the left. The authors agree with Jasper and Raney (1937) that factors responsible for the development of one highly integrated functional region might well favour a similar development of other such regions on the same side. If aphasia following right-sided lesions were as infrequent in left-handers as in right-handers this would tend to indicate the complete independence of handedness and language laterality.

DIFFERENCES BETWEEN LANGUAGE LATERALITY AND HANDEDNESS

A further examination of the accumulated data from this and other studies leads to the identification of properties of language laterality which are distinct from those of handedness.

As far as we know, there is no way of identifying language laterality by observing normal language behaviour. Its characteristics have been inferred only from the performance of patients with damaged brains, where the side of the lesion was known. Focal epileptic discharges accompanied by aphasia have given additonal clues. Electrical stimulation of the cortex has been shown by Penfield and his associates (1954) to produce temporary

aphasia similar to that which follows the removal of the brain tissue at the site of stimulation.

Language laterality also differs from handedness in that it is not defined in terms of discrete acts, some mediated by the left and some by the right hemisphere. Rather, each language performance is usually conceived of as arousing associative activity in both hemispheres, though to an unequal degree. This imbalance in the participation of the two hemispheres may vary from one modality of communication to another (speaking, reading, writing) and, as Jackson believed, between propositional speech on the one hand, and automatic or emotional speech on the other.

Constitutional and Cultural Factors in Laterality

Blau (1946) cites anthropological evidence which indicates that handedness is less strongly developed among primitive people who do not use many implements. In his own investigation he found that the more highly skilled an act was, the more reliable it was as an indicator of an individual's over-all handedness. The emergence of hand preference is a function of the opportunity for activities in which one hand must be used alone, chiefly in the manipulation of small objects. It is therefore based on the consensus of many separate manual habits, all originally subject to voluntary control and to influence by environmental pressure.

Neither social pressure to prefer the right hand, nor the great susceptibility of either hand to training, prevents a certain number of children from using the left hand for most skilled manipulations. Inspection of the statistics on the distribution of left-handed individuals leaves little room for doubt that heredity plays a role in hand preference. Brain (1945) cites the following data of Chamberlain's on the incidence of left-handedness:

Both parents right-handed	2·1%
One or both parents left-handed	17·3%
Out of a group of 33 families having both parents left-handed	46·0%

The manner of inheritance is not known. Gates (1946) cites Rife as considering "handedness as essentially a quantitative character due to more than one pair of factors."

While genealogical studies of handedness are possible, it is hardly possible to trace familial tendencies in the cerebral lateralization of language function. This can be inferred only in those individuals who develop or fail to develop aphasia with a unilateral lesion. In his paper, "Stockbrainedness," Kennedy (1916) shows that right-handed individuals

with crossed aphasia may come from families where left-handedness was predominant and vice versa. In these cases, it is the subject's own hand preference which has supposedly deviated from the expected trend. However, Mendel's (1912) description of a right cerebral lesion causing aphasia in a completely right-handed setting, indicates that the cerebral language laterality is as apt to deviate from the tendency of the stock as is the hand preference. In 3 of our cases of crossed aphasia in left-handed individuals, the family background is known, and in all 3 cases there is sufficient evidence of left-handedness to make Kennedy's theory inapplicable. This is also true of Tilney's (1936) own crossed aphasia and right hemiplegia. He and a grandmother, mother, brother, and son, were left-handed.

Flexibility of Language Laterality

Evidence from patients with congenital defects of the left cerebral hemisphere indicates that cerebral laterality does not depend on a predetermined localization of function on one side. Injury to the area which is originally more efficient can reverse the balance and, by causing the other side to become the relatively more efficient, lead to establishment of laterality on the side which would naturally have been the minor one. Thus, of the 10 hemispherectomized right hemiplegics reported by Krynauw (1950) (from 2 years, 9 months, to 21 years of age) none suffered any language disturbance after operation, and several improved markedly in speech as a result of it — even to the point of better than average achievement. In these cases of congenital left brain injury, as Gooddy and McKissock point out (1951), "The familial handedness changes sides. The naturally dominant eye and limbs take second place, though not necessarily far behind. The child continues to grow, to learn, and to act."

A shift in laterality for language is also assumed to be possible later in life. The extent to which the other hemisphere approaches the activity of the originally major area apparently depends on individual differences in potential, on the age of the individual, and the suddenness with which the major area fails. Thus, permanent aphasia is rarely seen in children after injuries to the left hemisphere. We do not know the age up to which such recovery may occur easily without a long period of re-learning. We know, however, that there is considerable flexibility in the acquisition and loss of speech automatisms, because before the age of 9, children who become deaf and are not forced to continue using speech will forget it, and will have to be re-trained. This lack of fixation of speech patterns is probably related to the amazing readiness with

which children learn new languages and discard old ones. It may also be related to the observation (Freud and Rie, 1891; Sachs, 1926) that aphasia follows right-sided lesions in children much more frequently (about 25 per cent) than in adults.

A more disputable point is whether cerebral language laterality can be influenced by a forced change in hand preference. Needles' (1942) discussion of this problem permits no definite conclusion. It is virtually impossible to present absolute proof that a change of laterality for language function has taken place in any case as a result of a change in hand preference. Such proof would require evidence of the original language laterality in the brain—evidence which can come with certainty only from the results of a brain injury. Two cases are reported in the literature (Oppenheim, 1899; Lovell, Waggoner and Kahn, 1932) of individuals forced to change handedness by injury to the right hand, at ages 10 and 17, and who were later rendered aphasic by right cerebral lesions at ages 31 and 59 respectively. In both cases only the history of right-handedness supports the assumption of original left cerebral language representation. In view of the comparatively great number of cases in which lifelong hand preference has failed to carry along language dominance in the brain, these two cases are not convincing. They could easily be among the number in which language originally preferred right cerebral activity or in which both hemispheres were active.

In the mature individual, the participation of the right hemisphere in speech is apparent in the partial recovery of the aphasic with a left-sided lesion. A new lesion in the right hemisphere will again make him aphasic, but a repeated lesion in the left hemisphere will also make him aphasic again. Such cases have been observed by Gowers (1893) and Nielsen (1946). Henschen (1922) has pointed out that the performance of the right hemisphere is always inferior, but no attempt will here be made to discuss whether this activity constitutes a true substitution or a partial return of premorbid functioning.

Statistical Distribution of Handedness and Language Laterality

Estimates of left-handedness in the population cluster around 5 per cent. Surveys tend to find decreasing frequency of left-handedness with increasing age. Moutier (1908) estimates left-handedness to be present in at least 10 per cent (about 9 per cent in his own observation) of the population; he also states that he found among 600 old people one ambidexter in 45. Other writers do not give figures on the incidence of ambidexterity, but it would appear less frequent than left-handedness, if we do not consider as ambidextrous those individuals who have been forced

to write with the right hand, and who prefer the left for other skilled acts. The distribution curve for handedness in the population would appear bimodal with the major concentration for right-handedness, a very much smaller concentration for left-handedness, and a dip in the centre for ambidexterity. Expressed in graphic form, this distribution might be presented as in fig. 1.

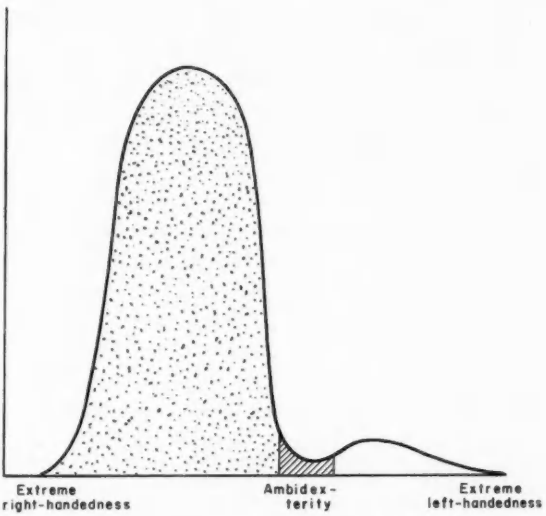

FIG. 1.—Hypothetical distribution of degrees of right- and left-handedness.

The proportion of people who have aphasia as a result of right hemisphere lesions is very small. Wepman (1951) cites from the literature a total of more than one thousand cases of brain injury with and without aphasia, in which no instance of left hemiplegia with aphasia was noted. This is an unusual figure because, if the cases were unselected, about 50 should have been left-handed, and it seems reasonable that some of these should have had a right cerebral lesion. It seems remarkable that none of them should have had an aphasia. A strongly contrary finding on the incidence of crossed aphasia in right-handers was reported by Ludwig (1939) on the basis of 880 right-handed German World War 1 veterans with right brain injuries, but otherwise unselected. One hundred (11 per cent) of these had aphasia, and about 30 of this number (3 per cent of the total) had aphasia lasting more than three months. Ludwig found that the frequency of aphasia following right-sided injuries, in left-handers and ambidexters (27 per cent), was only about two and a half

times as great as for right-handers (11 per cent). He does not report on the permanence of the uncrossed aphasias in left-handers. Nielsen (1951) gives 6 per cent as the frequency of crossed aphasia for right-handers and left-handers.

Humphrey and Zangwill's data (1952*a*) indicate that 9 of their 10 cases of left-handed individuals developed some aphasia after unilateral lesions of the language areas of either hemisphere. This is also true in 10 of 13 of our left-handed cases. Conrad (1949) presents still stronger statistical evidence to the effect that, including all cases with brain lesions, left-handers are more frequently made aphasic by unilateral lesions than right-handers. Out of a total of 760 brain-injured right handers, 26 per cent (198) had a history of aphasia. However, 38 per cent (18) out of a group of 47 left-handers were aphasic, at least temporarily. Such a difference in proportion could occur by chance less than six times in one hundred. This suggests that the situation with most left-handers is one of significant participation of both hemispheres in language.

Conrad also found that left-handed patients frequently had only a transitory language loss where the nature of the injury would lead to the expectation of a more profound loss. He concludes that left-handedness implies less fully developed specialization of either cerebral hemisphere. This possibility of a transitory aphasia from either side in a left-hander, if confirmed, should be of interest to the neurosurgeon. It would also demonstrate the inter-relationship of the two hemispheres in language because there should be no aphasia if language were represented bilaterally and independently. Subirana (1952) believes that when aphasia is absent or transitory "in all apparently contradictory cases," there is no true or exclusive cerebral dominance. Statistical analysis of Conrad's figures reveals no significant difference between left- and right-handed patients in percentage of transient aphasias. But statistical analysis does not take into account the severity of the lesion in the individual case, on which Conrad based his impression. The experience of the present authors in screening the cases in their own series parallels that of Conrad. Only 5 left-handers were discovered among 244 cases who had speech disturbances severe enough to cause them to be referred to the Aphasia Unit. On the other hand, 7 left-handers (Appendix cases 7 to 13) were discovered in the group of 76 epileptics with unilateral lesions of the anatomical language areas. Of the 5 who had an aphasia, only 1 had detectable aphasic residuals one year after injury, the remaining 4 having had only partial and transient language disturbances.

Roberts' (1951) figures on left-handers who have undergone cortical excisions indicate a much smaller proportion of right hemisphere language

participation than data collected from other sources. He reports only 3 aphasics out of 23 operated upon in the right hemisphere, against 13 out of 18 operated upon in the left hemisphere. Roberts does not state whether all of his cases involved excisions of the language areas. However, he also reports a similar low proportion of left-handers who demonstrated speech disturbance on electrical stimulation of the right hemisphere. This reminds one of Riese's (1950) remark that "the occurrence or absence of aphasia or apraxia after unilateral lesions does not admit of any conclusions as to dominant processes in the intact hemisphere."

The speech disturbances resulting from both electrical stimulation and cortical ablations differ in important respects from the effects of vascular lesions, tumours or injury. Thus, Roberts reports no systematic difference in the kinds of aphasia produced by excision or stimulation of different areas of the brain. Penfield and Jasper (1954), and Roberts (1951) report that cortical areas previously found responsible for aphasia when they were damaged (e.g. the insula) have no such effect when removed operatively. Thus the picture of language laterality obtained from cases of vascular or traumatic aphasia may be much different from that contributed by controlled stimulation or excision.

The best evidence for strong right hemisphere language laterality is the destruction of the left hemisphere language areas without consequent aphasia. There are in all our collected material only 8 such cases out of 61 left-handers with left-sided lesions. This may indicate that strong right hemisphere language laterality is infrequent even in left-handers. This is in contrast to the specialization of the left hemisphere for language in right-handers, as evidenced by the rare incidence of aphasia with right-sided lesions and left hemiplegia.

A theory which comes close to fitting these facts was offered by Bramwell (1899), who is better known for taking the position that crossed aphasia in left-handers was an "exceptional" condition which had to be explained by their training in right-handed writing, or by familial right-handedness. He suggests that there is a universal tendency to revert to left-brained speech as the natural or "original" condition of the species—a view which makes his other explanations unnecessary. Bramwell does not, however, go on to point out that regression of left-handers to the "original" left-brainedness for speech does not make them right-handers in spite of enforced training in writing with the right hand.

The addition of this observation transforms Bramwell's theory into one which is entirely congruent with the position of the present authors; i.e. the tendency for language to centre predominantly in the left hemisphere is in large measure independent of handedness; it is more nearly universal

than the tendency to right-handedness; it therefore operates to make many left-handers left-brained speakers, while the reverse condition is very rare.

From the evidence presented it appears that the distribution curve of language laterality differs from that of handedness by being more one-sided, unimodal, and tapering off, with more people showing cerebral ambilaterality for speech than there are having a clear-cut right-sided language dominance (see fig. 2). This independence of distribution from

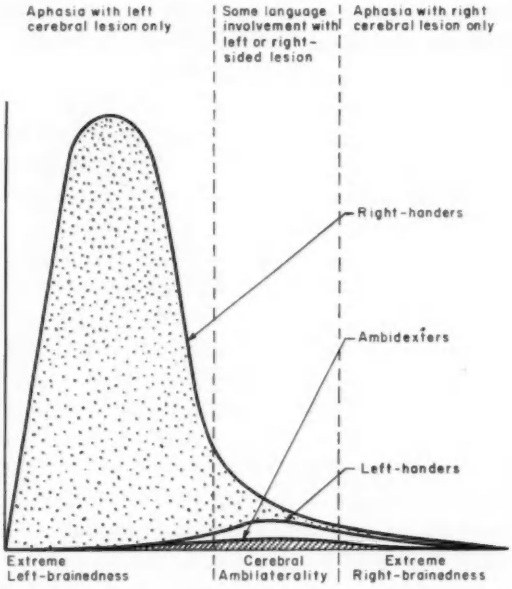

FIG. 2.—Hypothetical distribution of cerebral laterality for language among right-handers, ambidexters, and left-handers as inferred from the frequency of aphasia after unilateral lesions.

that of handedness means that laterality for language is not identical with laterality for handedness. Handedness does not determine brainedness.

LATERALITY, SPEECH AND LANGUAGE DISORDERS

There is no room here for an exhaustive treatment of the question of the relation of laterality to developmental disorders of speech or reading, but a review of the evidence is relevant to the topic of this paper. The observation has been made repeatedly by Orton (1937), Dearborn (1940), Harris (1947), and many others that stammerers and poor readers show a greater-than-average incidence of left-handedness, ambidexterity, and

mixed hand and eye preferences. This relationship must now be accepted as a fact to be explained.

An increased incidence of mixed or left-sided preference is a repeatedly verified finding for stutterers who have no known brain damage and whose verbal intelligence may be above average. Here, however, there is a question of interference with innervation at a level which is better considered one of speaking, in a narrow sense, than an interference with language on a symbolic level.

Speaking of unrecognized minimal birth injuries to the brain, Geseil and Amatruda (1941) state: "The type which expresses itself in speech difficulties, poorly defined unilateral dominance, and in delayed integration, may later result in a serious difficulty in the acquisition of reading." Some minimal brain injury at or after birth, or mal-development may affect one or all phases of language while leaving the rest of the intellect intact. This is in our opinion the explanation for some specific disabilities, such as circumscribed reading and spelling defect, partial amusia (poor ability to recognize, appreciate and perform music), poor spatial orientation, poor sense of rhythm, and others. There is little justification for regarding mixed or left-sided hand-eye preference as the primary cause of a predisposing factor towards a deficiency in acquiring language. This coincides with Brain's (1945) opinion, seconded by Subirana, that "anomaly of handedness is a symptom and not the cause of the disorder underlying the congenital aphasias."

An example of flexibility in the laterality of agnosic symptoms generally attributed to one hemisphere is the localization of lesions producing visual-spatial disorientation. McFie, Piercey, and Zangwill (1950) present 8 cases, and Hécaen, Ajuriaguerra, and Massonnet (1951) present six more in which disturbed visual-spatial performances occurred in right hemisphere lesions in right-handed individuals without aphasia. Brain (1941), Hermann and Pötzl (1926) and Humphrey and Zangwill (1952*b*), present cases of originally left-handed persons who had marked visual-spatial disorientation with right cerebral lesions and aphasia. Milner (1952) reports visual-spatial defects consistently more severe in right temporal lobe excisions than left. She suggests that this is a function which is usually lateralized on the right. This disorder is also known to occur with left-sided lesions in right-handed individuals, or with bilateral lesions, as Critchley (1953) points out. These samples show that there is no fixed laterality for these disturbances, nor is localization determined by laterality for handedness or laterality for language.

On a Theory of Lateral Specialization

We know, from cases with congenital right hemiplegia and severe left

hemisphere damage, that the right hemisphere alone can mediate the normal use of language. Why then should this function develop asymmetrically, preferring the left hemisphere in the intact brain? To say that language laterality results from the use of a preferred hand would require universal correspondence of hand and language laterality, which is not the case. The external and voluntary elements in the choice of hand preference are so obvious that some, like Blau (1946) have chosen to lay the entire phenomenon of handedness at the door of cultural determination. However, the hypothesis of cultural determination of handedness is heuristically valueless for understanding the asymmetry of language laterality in the brain, since this is beyond the reach of direct cultural influence. Thus, whatever weakness there may be in the case for constitutional determination of hand preference, no other plausible explanation has yet been forthcoming for language laterality.

No theory of lateral specialization has yet been offered to account for these facts: (1) Either hemisphere can function alone for language if the other is severely damaged early in life. (2) In children, aphasia from right-sided lesions occurs more frequently than in adults. (3) In children aphasia is more often transitory. (4) Left-handed people are possibly more susceptible to aphasia from lesions of either hemisphere than are right-handed. (5) The specialization of the left hemisphere for language in most right-handers is much more extreme than specialization of either hemisphere in left-handers. (6) The period of consolidation of language laterality in childhood is one of increasing learning ability in both verbal and non-verbal areas; thus the consolidation does not constitute a cessation of learning ability.

The ideal theory of cerebral laterality would permit us to start with two potentially trainable language association systems, differing slightly in their readiness to learn. The theory would have to allow for individual differences in the amount of imbalance between the two hemispheric systems, with inheritance tending to favour that on the left, especially in right-handers. Finally, and most important, the ideal theory should show how, after beginning with almost equal bilateral participation, a self-reinforcing process causes the slight lead in language performance to snowball into a nearly complete unilateral representation.

ORIGINAL CASE DESCRIPTIONS

Case 1.—Right hemiplegia with aphasia: R. S., aged 19, received a left frontal penetrating missile wound May 25, 1951. On operation three missile tracts, all within the left cerebral hemisphere, were found, although X-ray later showed one fragment lodged in the right posterior parietal area. On examination six months later the patient showed a right homonymous hemianopsia with macular sparing, right central facial weakness, right hemiplegia, hyperactive deep tendon reflexes.

and pathological reflexes on the right. Pneumoencephalogram showed the left ventricle dilated in the anterior horn and a normal right lateral ventricle. EEG showed a slow wave focus in the posterior portion of the left hemisphere and smoothing of the wave forms over the left central temporal area. At this time the patient had a severe mixed aphasia, with a marked articulatory component, and he was almost totally alexic and agraphic. He could evoke only a few single words in response to pictures or questions. During attempts to repeat back any but the simplest spoken words, he often perseverated with the same jargon-like utterance. He wrote his name easily and rapidly with his preferred left hand, and he later revealed that he had been taught to write with his right, but had reverted to the left in the fourth or fifth grade. The patient's mother verified that she herself was left-handed, as were the patient and his brother. Six other children and the father were right-handed.

In May 1952, after six months of re-training, the patient had a great many words available for spontaneous speech, but was still unable to use sentences, and had moderate articulatory difficulty. Comprehension of speech was now almost normal, but only slight gains in written word-recognition and spelling were measured on re-testing.

Case 2.—Right hemiplegia and aphasia: C. M., aged 47, developed a right-hemiplegia and severe aphasia in the course of treatment for osteomyelitis of the left tibia. A diagnosis of "encephalomalacia of the left internal capsule and thalamus due to vasospasm and thrombosis," was made at that time. When admitted for language re-training in January 1948, a pneumoencephalogram showed dilatation of the left ventricle in an otherwise normal ventricular system. EEG showed abnormal focal activity in the left temporo-occipital area. His right hemiplegia had receded sufficiently for the patient to resume writing with his right hand. He gave a history of left-handedness from birth, and stated that he had been forced to learn to write with his right hand. He had readily taken to the use of his left hand for writing during the period of severe hemiplegia.

His aphasia had improved greatly up to the time of his admission and was principally sensory in nature. He had fairly fluent speech, with normal articulation and inflection. However, there was still groping for words, and circumlocution in his speech. He understood spoken commands poorly, had a severe word-deafness for words spoken out of context, and had considerable difficulty in following conversation. He also had a great deal of spelling difficulty, and when words were dictated he would repeat them aloud, over and over, without appearing to understand what he was saying. Even with this device he would forget the word or wander to another within the same sphere of meaning. After a year and a half of treatment, his understanding of conversation and writing ability had improved, but he still had trouble understanding isolated words.

Case 3.—Right hemiparesis and aphasia: F. F., aged 48, was admitted to the medical service of the hospital on April 23, 1951, because of the onset, three days before, of right hemiparesis and aphasia. The patient had had seven previous admissions for kidney disease, and for a skin ailment. At the time of his sixth admission, in April 1949, signs of an old vascular accident in the *right* hemisphere were discovered. These included dragging of the *left* leg, sustained patellar clonus and Hoffman sign on the left. The left arm was slightly clumsy. The patient reported that he had noticed the onset of numbness and weakness in his *left* arm a year before—at the same time that his *left* leg felt funny and started to drag. An EEG performed on April 26, 1949, was within normal limits. No speech disturbance was noted, and none was reported by the patient.

At the time of his most recent admission he was reported to have fallen to the floor without losing consciousness, having weakness of the *right* side, with the right

corner of his mouth drooping. He showed a predominantly sensory aphasia, speaking in phrases with normal rate, inflection, and articulation, but with considerable paraphasia and word hunting. He had difficulty in following spoken commands, and could not read or write. Neurological examination in August 1951 showed that the old signs on the left side of the body were most prominent, while strength on the right had been regained. However, an EEG performed in May 1951 revealed a slow wave focus in the left anterior frontal area.

The patient reported that he was left-handed in all respects except writing. He claimed that he used to prefer his left hand for writing, but was forced to use his right in the early grades. His mother was also allegedly left-handed, except for writing.

In December 1951, language examination revealed that the patient's speech was superficially normal, but there was moderate anomia and a great deal of circumlocution because of it. His own sentences often trailed off in confusion, but he now understood commands and conversation well. Reading comprehension was recovered to the third-grade level of efficiency, and writing had returned to a greater degree during six months of re-training.

Case 4.—Left hemiplegia and aphasia. V. R., a 29-year-old female patient, with severe left hemiplegia and aphasia, was admitted for speech re-training in September 1951. She had suffered severe cerebral contusions in an automobile accident in November 1950, which had been followed within forty-eight hours by left facial paralysis and left hemiplegia. Two days after injury, while still in coma, bilateral trephination revealed brain œdema, but no sign of hæmorrhage. After this procedure, a right facial paralysis and paresis of the right arm developed and then receded, while the patient remained in coma for two weeks.

Examination in September 1951 revealed a spastic left hemiplegia and a left facial weakness of the central type, hyperactive deep reflexes, Babinski, and Oppenheim sign on the left. There was diminished sensation to touch, pain, and vibration on the left side. The right pupil was smaller than the left, and there was a ptosis of the right eyelid. Pneumœncephalogram done on May 12, 1952, revealed marked dilatation of the lateral and third ventricles without a shift in the ventricular system. Increased amounts of air were seen in the subarachnoid channels, and the interpretation of extensive brain atrophy was made. EEG with metrazol activation, performed in May 1952, showed a low metrazol threshold without a clear focus, while a sleep record later that month showed a lack of sleep spindles and of arousal responses on the right, indicating extensive damage in that hemisphere. Later that month the patient reported her first focal seizures, involving the left arm.

The patient reported that she had been left-handed before her injury, and her family advised that she and one of her brothers were completely left-handed, while the remaining three siblings were right-handed.

Upon admission to the aphasia service, the patient had a moderate mixed aphasia, revealing a varied vocabulary of single words and short phrases, which she used in answering questions, but she almost never initiated speech. She had word-finding difficulty for all categories of words, and made frequent paraphasic word substitutions in tests for evoking single words in response to pictures, printed or spoken cues. Her understanding of spoken language in tests was defective to the point of mismatching some spoken words and pictures, and misinterpreting simple commands. Her understanding of conversation was less obviously impaired. With regard to written language, the patient recognized the meanings of many individual words, but had no success with sentences. The patient could write nothing beyond her name from dictation, but was able to write "cat" and "man" on presentation of a picture stimulus. She was completely acalculic. Aphasia, in this case, can clearly be attributed to the right cerebral lesion, if these facts are considered:

There was no speech before patient came out of coma two weeks after the injury. There was bilateral dilatation of the ventricles, but it seems not likely that the aphasia would have been so severe if it were part of the transient signs observed on the right (right central facial weakness, and weakness of right arm) after trephination. All later examinations, neurological and electroencephalographic, reveal a lesion in the right hemisphere, and fail to reveal evidence for a lesion on the left.

After eight months of therapy, re-examination revealed that her command of spoken vocabulary for spontaneous speech had improved measurably, although her sentence structure was still telegraphic for any but the shortest sentences. Her understanding, while slightly improved, was still defective. Intensive practice with written language had made little inroad into her alexia and agraphia. Although she acquired good right-handed writing, and would copy and memorize sentences with key words, her retention was barely adequate for one day, and she still failed to score on standardized reading or spelling tests.

Case 5.—Right hemiplegia and aphasia. H. C., a 45-year-old male, was hospitalized in December 1953 for control of epileptic seizures. On neurological examinaton he had a mild, right, residual hemiplegia, and a moderate mixed aphasia, with dyscalculia. The history revealed that he had become aphasic in 1942, during his hospitalization for an appendectomy. At that time he had developed thrombophlebitis, followed by cerebral thrombosis, and acute arterial occlusion of his right leg, which led to a low thigh amputation. During the next eight years he received intensive speech re-training.

While the patient currently referred to himself as "ambidextrous," his handedness history revealed that writing was the only activity in which he had preferred the right hand. He had been converted in school from his original inclination to use the left hand in writing. There were no other known left-handers in his family.

Case 6.—Right temporo-parietal lesion without aphasia. C. P., a 27-year-old machinist was hospitalized on March 24, 1954, with complaints of headache of ten days' duration, and a momentary lapse of consciousness during which he had driven his automobile into a tree just prior to hospitalization. Neurological examination revealed bilateral papillœdema, left homonymous hemianopsia with macular sparing, and left supranuclear facial paresis. There was no weakness. Tendon reflexes were increased on the left, but there were no pathological reflexes. There was no disturbance of co-ordination, but the left arm tended to pronate and move up and out. There were no sensory disturbances. Electroencepalogram revealed a slow-wave focus in the posterior portion of the right hemisphere. A right carotid arteriogram revealed tumour stain in the temporo-occipital area. Psychological examination revealed no aphasic defect in either spoken or written language at this time. A disturbance in reproduction of distances in vertical or forward direction was the only perceptual-motor deficit found. Higher mental processes were intact.

In view of the present findings and the history of excision of a melanoma of the chest two years ago, a right temporal craniotomy was performed on April 8, 1954. There was an extensive excision of tissue from the posterior temporal and parietal lobes with partial removal of a metastatic melanoma. No sign of language impairment was found on the day following operation. Five days later, speech and reading were again found to be intact.

The patient reported that he had always been left-handed for all activities, including writing. His mother and one sister are also left-handed, but his father, his three brothers, and his other sister are right-handed. After the radical removal of left chest muscles, with severe scarring near the left shoulder, the patient tended to develop his right hand in the past eighteen months. He was now using this hand predominantly in his work as a machinist. However, he continued to write with his left hand, and was extremely clumsy in attempts to write with the right hand.

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Case 7.—Monoplegia, left arm, and transient aphasia following right frontal brain injury. H. C., a 22-year-old officer was admitted to Cushing General Hospital, January 17, 1946, ten months after receiving shell fragment wounds of the brain, eyes, and left arm. At operation, the day after injury, there was found a compound comminuted fracture of the right frontal region with extrusion of the frontal lobe. Patient was unconscious for twelve days following the injury, and then was found to have paresis of the left arm and aphasia, which cleared in six weeks. No details of the speech disturbance available. He suffered the first of a series of lapses of consciousness without convulsions in November 1945.

On examination in January 1946, he was found to be blind in the left eye, with metallic foreign bodies in the orbit. There was mild atrophy and weakness of the left arm and, in addition, a complete left ulnar nerve paralysis, the latter due to the wound in the arm itself. Neurological examination revealed no reflex changes, motor or sensory abnormalities, except those of the left arm and hand. Electroencephalogram revealed a slow wave focus in the right fronto-temporal area. A pneumoencephalogam made in August 1945 had revealed marked dilatation of the ventricular system and especially marked dilatation upwards of the body of the right lateral ventricle. No residuals of aphasia could be found on detailed examination in June 1946.

The patient had been predominantly left-handed, and had always written with the left hand, although he preferred to bat a ball in right-handed fashion. In the fifteen months since injury he had learned to write easily with the right hand.

Case 8.—Left hemiparesis and aphasia after right-sided injury. O. L., a 24-year-old soldier was transferred to Cushing General Hospital in January 1946 with a history of a right temporo-parietal penetrating injury received in March 1945. The shell fragment had traversed the right lateral ventricle and lodged in the medial wall of the ventricle. Patient remained unconscious for thirty-six hours, and was operated on ten hours after the injury. On examination, left hemiplegia, left homonymous hemianopsia, and motor aphasia were found. The patient reported he remained severely aphasic for two months. He also suffered *grand-mal* seizures from the time of injury.

On examination in January 1946, slight articulatory difficulty was found, without definite aphasic residuals. Neurological examination revealed left hemparesis with hyperactive reflexes and positive Hoffmann, Rossolimo and Oppenheim signs on the left. Sensation was reduced in all modalities on the left side. No neurological abnormalities on the right. Electroencephalogram showed slight slow wave focus in the lower right parietal area with build-up on hyperventilation. Pneumoencephalogram of April 25, 1945, showed generalized dilatation of the ventricular system, most marked in the region of the right posterior horn. More air accumulated in the region of the right Sylvian fissure than the left.

The patient was completely left-handed before his injury. Familial handedness is not reported.

Case 9.—Right temporo-parietal wound without aphasia. P. M., a 32-year-old officer was admitted to Cushing General Hospital, February 21, 1946, with a history of a penetrating wound received in August 1944. At debridement, one hour after injury, depressed bone fragments and lacerated brain tissue in the right temporo-parietal region were removed. The patient was not unconscious at the time of the injury, and had no paralysis or sensory loss. However, he had no memory for events in the two-day period after injury, and he showed some confusion for four or five days. In January 1945 he had a first *grand-mal* seizure.

On examination in February 1946 there were no neurological abnormalities apart from deafness of the right ear. There was a skull defect measuring 3 by 3½ cm. in the right parietal region. Pneumoencephalogram of December 11, 1945, revealed very slight dilatation and possible displacement to the right of the posterior horn of

the right lateral ventricle. Electroencephalogram was abnormal with a slow wave focus in the right temporal area. No evidence of aphasia could be detected, although patient recalled a period of stuttering after his injury. His Verbal I.Q. was 133, Performance I.Q., 130.

The patient was left-handed by preference, using the left hand for writing until he was 15, when his father made him change to the right hand in writing. Family hand preference is not known.

Case 10.—Left hemiplegia and mild aphasia following right parietal injury. H. M., a 31-year-old soldier, was admitted to Cushing General Hospital, December 6, 1945, nine months after receiving a penetrating shrapnel wound in the right parietal area. Debridement was carried out twenty-eight hours after injury, and left hemiplegia and mild motor aphasia were found after recovery from unconsciousness lasting three weeks. He started having focal attacks in the left arm in June 1945, and *grand-mal* seizures with focal onset in the left arm, but without speech disturbances, in December 1945.

On examination in December 1945, patient had a hemiparesis of the left side, with increased tone, increased tendon reflexes, diminished abdominal reflexes, Babinski's and Oppenheim's sign on that side. Position sense in fingers and toes, two-point discrimination and figure-writing were disturbed on the left, but other sensory modalities were normal. Left homonymous hemianopsia was found at this time. Electroencephalogram was normal. Skull film showed no defects apart from metal plate over right parietal bone defect. Verbal I.Q., 133, Performance I.Q., 73.

Language examination revealed a stutter which patient claimed to have had all his life. A mild dysgraphia but no other aphasic residuals were found. The patient had been left-handed in all respects but writing, for which he always used the right hand.

Case 11.—Left hemiparesis and transient aphasia after right parietal injury. J. B., a 21-year-old soldier was admitted to Cushing General Hospital on December 11, 1945. On March 26, 1945 he had received a perforating shrapnel wound with entrance in the right parietal region and exit in the right occipital, and involving the frontal, parietal, temporal and occipital lobes. Craniotomy and debridement were performed the next day. Patient remained unconscious for four days, then was found to be hemiplegic on the left, mildly aphasic, and he had a left homonymous hemianopsia. *Grand-mal* seizures started in October 1945.

Neurological examination of December 1945 showed left homonymous hemianopsia, left spastic hemiplegia, increased tendon reflexes, positive Hoffman and Oppenheim signs on the left, and general reduction in all sense modalities on the left, including absent position sense. Electroencephalogram showed a slow wave focus in the right temporal area, and pneumoencephalogram in January 1946 showed generalized dilatation of the ventricular system, with marked enlargement and distortion of the right lateral ventricle. Language examination at this time revealed no aphasic residuals, apart from a slight spelling defect. The patient said that his word-finding difficulties cleared up a month and a half after his injury.

Patient had been completely left-handed before injury, but family's handedness was not given.

Case 12.—Transient right hemiplegia and mild aphasia following left frontal brain injury. J. M., a 24-year-old officer was admitted to Cushing General Hospital February 5, 1946, seven months after he was struck by a bullet in the left frontal region. The wound was debrided of bone fragments and macerated brain tissue on the date of injury. Patient had a right hemiplegia and mixed aphasia. His first *grand-mal* seizures occurred eight days later. Paralysis cleared within two months, but a mild word-finding difficulty persisted.

On examination in February 1946, neurological examination was normal throughout. Skull film revealed the metallic plate covering the frontal bone defect. Electro-

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encephalogram showed a borderline dysrhythmic record without definite focus. Mild aphasic hesitancy in speech was still observed at this time, but there was no defect in written language.

The patient reported he performs most skilled acts with the left hand, but writes with his right. No report of family handedness is available.

Case 13.—Left temporal lesion without aphasia. J. J., a 24-year-old soldier was admitted January 16, 1946, having received a gutter type wound of the left temporal region on June 18, 1944. He was unconscious for three days, and upon awakening he had a complete amnesia for his past life and spoke slowly with a stutter. In October 1944 neurological examination was essentially negative with the exception of a partial peripheral left upper facial nerve paralysis. Pneumoencephalogram revealed a slight dilatation of the left lateral ventricle. The patient was suffering from post-traumatic psychomotor epilepsy, consisting of periods of disorientation and confusion, with amnesia.

Examination January 1946 showed a peripheral paralysis of the left frontalis muscle, and bilaterally reduced auditory acuity, while the rest of the neurological examination was negative. The patient continued to speak slowly, with a severe stutter. Detailed psychological examination led to the conclusion that the stutter was not a residual of any aphasia. Verbal I.Q., 127, Performance I.Q., 119.

Electroencephalogram performed September 5, 1945, following pitressin hydration, showed high voltage abnormal, slow activity directly overlying the skull depression in the left temporal region. Routine electroencephalogram of January 22, 1946, was normal.

The patient reported himself as naturally left-handed, except for writing. He was forced to use the right hand when he started school. No information was given as to handedness in patient's family.

Ballantine's Case (*See Bibliography*).—This patient and her mother were interviewed by the authors in January 1954, through the courtesy of Dr. Ballantine, and the following supplementary information was obtained. The patient now had a right hemiplegia, spoke and understood normally, but reported some slowness in reading. Her post-operative aphasia had lasted six months, and was chiefly amnesic in character. Her original dysgraphia cleared rapidly.

This patient had always been extremely left-handed in all activities, including writing. She had noticed as a child that she could do manœuvres in dancing with her left foot, which were awkward with the right. Several trials at sighting with both eyes open revealed that she was right-eyed, however.

The family history was one of left-handed preference on the part of two brothers for most activities. Neither brother is as strongly left-handed as the patient. The patient's mother was predominantly right-handed, but had observed more than usual left-sided motor facility in herself. Her father (patient's grandfather) had been ambidextrous, but all of the eight siblings were right-handed. The patient's father is right-handed.

Short Description of Cases of Left-handers with Lesions of Language Areas

Group 1.—*Left-handers with Right Cerebral Lesions and Aphasia,* 50 *cases.*

Jackson (1866).	Left hemiplegia and aphasia in a man who had previously suffered right hemiplegia without speech defect. Left-hander, but no mention of writing hand or ætiology.
Jackson (1868).	Severe aphasia with left hemiplegia. Patient was left-handed but wrote with right hand. His four children by first wife were left-handed; two by second wife were not. No information on ætiology.

Wadham (1869).	18-year-old boy; left hemiplegia and severe aphasia. Patient wrote with left hand and had four left-handed brothers. Autopsy: Island of Reil on right replaced by fluid-filled cavity. Left hemisphere intact.
Ogle (1871).	(Three cases). Three cases of left hemiplegia with aphasia in left-handers out of a series of 100 aphasic hemiplegics.
Russell (1874).	69-year-old man. Sudden onset motor aphasia and left hemiplegia. Patient had learned to use right hand for writing with great difficulty. No information on ætiology.
Kussmaul (1877).	66-year-old, well-educated man, left-handed, except for writing. Left hemiparesis and rapidly worsening sensory aphasia, agraphia. Autopsy: Egg-sized softening right anterior temporal lobe. Second lesion from Sylvian fissure to caudate nucleus.
Cuffer (1880).	Left hemiplegia and sensory aphasia; rapid recovery. Patient wrote and ate with right hand. Otherwise left-handed. Onset after confinement with third child.
Habershon (1880).	52-year-old man. Progressive motor aphasia for seven weeks, followed by death. Autopsy: Glioma of right insula and posterior part of third frontal convolution. Life-long left-hander. Not known if he used left for writing.
Jackson (1880).	Sailor with sudden onset of left hemiplegia and aphasia, presumably of vascular origin. Patient was left-handed, except for writing and sewing sails, in which he was forced to use the right hand.
Dally (1882).	Left hemiplegia and aphasia, following apoplectic attack. Wrote with paragraphic errors. After two years, speech and reading recovered but spelling defective.
Féré (1885).	Left hemiplegia and aphasia. Patient used right hand for writing. No details regarding ætiology or duration of aphasia.
Hale White (1887).	50-year-old, left-handed woman. Left hemiplegia and aphasia. Autopsy: Hæmorrhage into left internal capsule and lenticular nucleus.
Bell (1895).	Left hemiplegia and aphasia probably due to embolus caused by mitral insufficiency. Died two days after onset. No autopsy.
Runeberg (1898).	Case of motor aphasia with left hemiplegia in a left-handed woman consequent to thrombosis of arteria fossæ sylvii.
Köster (1899).	Left-handed Bright's disease patient of 40. Progressive left hemiplegia and amnesic aphasia, agraphia, left hemianopsia. No definite word deafness. Autopsy: Softening of entire Sylvian area.

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Zilgien (1906).	Left-handed man with aphasia (type unspecified), Jacksonian seizures, crying spells. Autopsy: Diffuse meningo-encephalitis with area of softening in right lower Rolandic region.
Mingazzini (1910).	60-year-old man, life-long left-hander suffers sudden left hemiplegia and complete aphasia, improving to partial sensory aphasia. Autopsy: Destruction posterior portion of insula on right and of dorsal portion of the gyrus temporalis profundis.
Dejerine (1914).	Illiterate man becomes aphasic and remains so four years until death. Autopsy: Massive destruction of right hemisphere.
Dejerine (1914).	Aphasia with recovery, in a left-handed patient who wrote with right hand. Autopsy: Such severe destruction of right hemisphere that the recovery of speech must be attributed to substitution of left hemisphere.
Head (1926).	Traumatic right cerebral lesion with semantic aphasia, no hemiplegia.
Weisenburg and McBride (1935).	Tumour, right fronto-temporal. Nearly complete aphasia and left hemiparesis post-operatively. Patient completely left-handed.
Chesher (1936).	(Two cases.) Tumours: Discrete lesions in right hemisphere language areas with aphasia, type unspecified. Both cases pure left-handers.
Chesher (1936).	(Three cases.) Tumours of right hemisphere language areas with aphasia, type unspecified. Presence of hemiplegia not indicated. All were left-handed except for writing. Classified by Chesher as having mixed handedness.
Brain (1941).	Right parieto-occipital abscess. Mixed aphasia. Also has minor hemisphere syndrome with respect to neglect of space on one side.
Kennedy (1947).	Right cerebral injury with left hemiplegia, complete motor and partial sensory aphasia for two years, improving with therapy. Pneumoencephalogram and exploratory trephination verify right frontal hæmatoma and cerebral atrophy.
Nielsen (1948).	Right CVA with left hemiplegia and aphasia with good recovery. Later left CVA and right hemiparesis with agraphia for right hand only. Patient had used right hand since childhood for writing.
Conrad (1949).	Right occipital penetrating gun-shot wound and transient aphasia. No hemiplegia.
Conrad (1949).	Right parietal lesion with left hemiplegia and transient aphasia.
Conrad (1949).	Right parieto-temporal lesion with left hemiplegia and motor aphasia.
Conrad (1949).	Right parietal lesion with sensory aphasia and right [sic] hemiplegia.

Conrad (1949).	(Two cases.) Right central lesions, one motor and one sensory aphasia. Both have left hemiplegia.
Conrad (1949).	Right fronto-temporal penetrating wound with sensory aphasia; no hemiplegia.
Roberts (1951).	(Three cases.) Right cerebral operations followed by aphasia in left-handed patients. No details on writing hand or on type or duration of aphasia.
Humphrey and Zangwill (1952*a*).	Right parieto-occipital trauma with mild mixed aphasia and minor hemisphere syndrome for neglect of space and dressing dyspraxia. Good recovery and adoption of right as preferred hand.
Humphrey and Zangwill (1952*b*).	(Three cases.) Right cerebral head wounds with aphasia; recovered. All with left hemiplegia. One wrote with left hand, two with right.
Present Authors.	(Five cases.)

GROUP II.—*Left-handers with Left Cerebral Lesions without Aphasia,* 8 *cases.*

Westphal (1884).	Left-handed patient with huge gliosarcoma of left temporal lobe and softening of island of Reil, without aphasia.
Chesher (1936).	Tumour in language area of left hemisphere without aphasia. Patient is strongly left-handed and from a right-handed family. (Presence of hemiplegia not mentioned.)
Conrad (1949).	(Five cases.) Left cerebral wounds of language areas without occurrence of aphasia. Three with paresis of right arm or arm and leg; two without.
Present Authors.	(One case.)

GROUP III.—*Left-handers with Left Cerebral Lesions and Aphasia,* 53 *cases.*

Paget (1887).	Left-handed pastor who wrote with right hand. Aphasia and right hemiplegia, after three successive vascular accidents.
Wood (1889).	50-year-old man with progressive mixed aphasia and right hemiparesis. Wrote with right hand but was otherwise left-handed for manual work. Autopsy indicates left-sided lesion, but no details given.
Dickinson.	49-year-old marine engineer admitted to hospital after a convulsion, resulting from blow on head. Complete motor aphasia and right hemiplegia, but continued to write fluently with left hand. Recovered completely in a few weeks.

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Bramwell (1899).	36-year-old left-hander who wrote with right hand. While straining at the stool was suddenly seized with right hemiplegia and severe motor aphasia with slight impairment of comprehension and written language. Remainder of family right-handed.
Miyake (1909).	4-year-old left-handed child. Developed aphasia with left cerebral lesion. Operation followed by recovery.
Liepmann (1912).	Left-handed woman admitted to hospital for hearing voices. Then suffers right hemiplegia, right hemianopsia, and severe disturbance of word-finding, reading and writing. Slight difficulty in repetition. Autopsy: Enormous lesion of third frontal convolution, central convolution, insula, temporal lobe, parts of external capsule. Right hemisphere intact.
Ardin-Delteil, Lévi-Valensi, Derrieu (1923).	Severe right hemiplegia, predominantly sensory aphasia, improving markedly over a five-week period, and presumably vascular ætiology. Patient strongly left-handed except for writing. Sister also left-handed.
Long (1913).	Right hemiplegia and sensory aphasia without motor aphasia following destruction of Broca's and adjacent areas.
Tilney (1936).	Left cerebrovascular accident with aphasia; agraphia most severe for the right hand. Patient had always written with right hand, but otherwise completely left-handed. Half of family also is left-handed. Complete recovery of speech and recovery of writing with left hand, with right hand remaining apraxic for writing.
Weisenburg and McBride (1935).	Tumour of left temporal lobe operated. Patient was left-handed except for writing and sewing. (Classified as ambidextrous by Weisenburg and McBride for this reason). Post-operative slight right hemiparesis; predominantly sensory aphasia.
Weisenburg and McBride (1935).	Exploratory operation, left temporo-parietal area. Patient (classified by Weisenburg and McBride as ambidextrous) was originally left-handed, but switched to right in school. Post-operatively right hemiparesis and marked, predominantly motor aphasia, which improved rapidly.
Weisenburg and McBride (1935).	Tumour left temporal lobe. Severe mixed aphasia post-operatively. Right hemiparesis. Patient completely left-handed.
Chesher (1936).	(Five cases.) Tumours of left hemisphere language areas. Patients are described as claiming to be originally left-handed, but to have acquired a number of right-handed skills. (Classified by Chesher as showing mixed-handedness.) No mention of type of aphasia or presence of paralysis.
Conrad (1949).	(Three cases.) Left cerebral lesions (traumatic) followed by transitory aphasia; two cases with right hemiplegia.

Conrad (1949).	(Seven cases.) Left cerebral lesions (traumatic) followed by severe aphasia; include four motor aphasics with right hemiparesis, one motor, one amnesic, and one sensory aphasic without paralysis.
Roberts (1951).	(Thirteen cases.) Left-handed patients who became aphasic after operation on left hemisphere. No details on writing hand or on type or duration of aphasia.
Wepman (1951).	(Two cases.) Left-handed patients with right hemiplegia and aphasia. No other details mentioned.
Humphrey and Zangwill (1952).	Penetrating head wound, left hemisphere. Permanent, severe dysphasia. Patient was believed to have written with right hand, but was otherwise strongly left-handed.
Humphrey and Zangwill (1952).	(Four cases.) Left cerebral penetrating head wounds with aphasia, recovered. Three hemiplegic, one hemiparetic.
Ballantine (1953) and personal communications.	15-year-old, completely left-handed girl operated for abscess of left parietal lobe. Moderate amnesic aphasia and dysgraphia, recovered after six months, with more persistent dyslexia and dyscalculia. Two brothers partly left-handed.
Present Authors.	(Five cases.)

GROUP IV.—*Left-handers with Right Cerebral Lesions of Language Areas without Aphasia*, 12 *cases.*

Kennedy (1916).	Penetrating, massive right-sided temporo-parietal wound, without an aphasic symptom. Patient was very strongly left-handed, even for eating, but used right in writing. Family was right-handed.
Kennedy (1916).	Skull fracture with bone defect in right temporo-occipital area; transient left hemiplegia, but no aphasia. No other left-handers in family.
German and Fox (1934).	Resection of right frontal lobe without speech involvement. Patient's family includes five left-handers, six right-handers. Patient was left-handed except for eating and writing.
Conrad (1949).	(Five cases.) Injury of language areas of right hemisphere without aphasic symptoms. Two with left hemiparesis and three without paralysis.
Humphrey and Zangwill (1952).	Severe mid-parietal wound on right without aphasia, simply a non-aphasic dysarthria. Had left hemiplegia.
Milner (1952).	Excision of right temporal lobe because of epileptogenic focus. No speech disturbance either on electrical stimulation of exposed cortex or after operation.
Present Authors.	(Two cases.)

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SUMMARY

(1) 110 cases from the literature and thirteen new cases of left-handers with unilateral lesions of the language area were collected.

(2) Language was found to be disturbed by lesion of the left hemisphere in 53 per cent of all left-handers.

(3) Cerebral laterality for language and handedness are not directly linked, and one does not determine the other; left cerebral laterality for language is more prevalent than right-handedness, and right cerebral laterality for language much less prevalent than left-handedness.

(4) Hypothetical distribution curves for handedness and language laterality are presented.

(5) The theoretical implications of the problem are discussed.

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RECOVERY FROM "MUSCULAR DYSTROPHY"

BY

F. J. NATTRASS[1]

(From the Department of Medicine, King's College, University of Durham and the Royal Victoria Infirmary, Newcastle upon Tyne)

Introduction

This study concerns a group of cases in which recovery has taken place from a disease in childhood closely resembling classical muscular dystrophy. The primary myopathies or muscular dystrophies are generally regarded as incurable diseases. It is, of course, recognized that the prognosis is different in the various types of myopathy, being uniformly grave in the Duchenne or childhood variety, but often compatible with a normal life span in the facioscapulohumeral type. Furthermore, a number of arrested or fragmentary cases have been described in which the disease has become stationary for many years or remained confined to individual muscles or groups of muscles. Improvement has from time to time been reported, and attributed to a large number of therapeutic agents; such improvement, however, has never amounted to complete recovery, and I share the general belief that these claims have not been substantiated by controlled trial of the remedies concerned. Nevertheless, personal observation and the knowledge of a small number of cases under the care of colleagues led me to believe that a fresh survey was desirable, using all needed accessory methods of diagnosis, with the object of determining what evidence there was of recovery occurring either spontaneously or as the result of treatment. Dr. John N. Walton joined me in this work and his energy and initiative carried the investigations beyond my expectations. They led us into the vexed field of classification, on which our views have been published (Walton and Nattrass 1954). The results of a therapeutic trial in 98 cases have been included in the same publication; they led us to the conclusion that none of the principal remedies hitherto used has any influence on the course of true muscular dystrophy.

It is then to the existence and nature of the small group of recoveries that I would ask your attention. We report eight patients who have

[1]Presidential Address to the Section of Neurology, Royal Society of Medicine, October 7, 1954.

recovered from a disease previously diagnosed as muscular dystrophy. These have come to light firstly in an attempt to follow up all cases of myopathy seen in the Royal Victoria Infirmary, Newcastle upon Tyne, since 1930: secondly, through information from the Ministry of Health who had been supplied with a list of members of a muscular dystrophy association formed in 1949: and one case was reported to us by Dr. Douglas Gairdner. All eight patients were interviewed and examined in 1951 and 1952: it must be stressed that at the time of this interview all had recovered either completely or almost completely. Only one was seen personally by me at the height of the disease, but the recorded observations and recollections of the family doctors and the physicians who made the diagnosis in the other cases were made available to us. Despite the resemblance of the clinical picture in all of these cases to that of progressive muscular dystrophy it now seems likely that none of the patients was suffering from this disease. Although it would be possible to refer to the condition in these cases as a "benign childhood myopathy" (Walton and Nattrass 1954) I shall give reasons for suggesting that the majority of the patients were suffering from polymyositis or dermatomyositis.

Review of the Literature

The possibility of spontaneous recovery from myopathy was first discussed by Batten (1910), and later received attention from Bramwell (1922–3). Batten reviewed 6 possible cases which had been previously reported; Bramwell referred to these same cases and reported another. Since these reports there have been no well-authenticated descriptions of spontaneous recovery, although numerous instances of alleged improvement, often considerable, have been described as a result of a wide variety of remedies, particularly vitamin E and its analogues (Bicknell, 1940; Stone, 1940; Rabinovitch, Gibson and McEachern, 1951). The fact that numerous other workers have failed to demonstrate the efficacy of any therapeutic regime, combined with scepticism as to the accuracy of the diagnosis in the cases of spontaneous recovery, probably accounts for the lack of attention paid to this subject in the recent literature.

The first reported case of apparent spontaneous recovery was described by Marina (1908) in a girl of 8. Two other children born subsequently appeared normal. This girl showed atrophy of the serrati, trapezii, supraspinati and upper half of the infraspinati, while the lower part of the infraspinati and the deltoids were hypertrophied: there was striking abnormal mobility of the scapulæ. The only significant abnormality in the lower limbs was some hypertrophy of the glutei. The child was again seen at the age of 14 when she seemed well developed and healthy. The

only abnormalities on physical examination were slight scoliosis, slight winging of the scapulæ and perhaps some persisting hypertrophy of the infraspinati and glutei. Marina regarded this case as one of almost complete spontaneous recovery from myopathy.

Another case was described by Armand-Delille and Weil (1906); a boy aged 7 had suffered from muscular weakness in the pelvic and shoulder girdles for some two months when he was first seen. Within twelve days of being examined he showed considerable improvement and recovery was complete nine months after the onset of the disease. Batten also refers to a case of myopathy with lipomatosis, showing improvement after treatment with pituitary extract, which was reported by Levi and de Rothschild in 1907; he suggested that the weight of evidence was strongly against a diagnosis of myopathy in this case and in that of Armand-Delille and Weil.

Probably the best authenticated case of possible recovery was that described by Erb (1908). An English child of 7 years was one of a family of three, the other children being healthy. The child's gait had been clumsy and he had tended to fall easily for about eighteen months. He had also developed considerable difficulty is rising from the floor and in raising his arms above his head. The muscles of the shoulder girdle were atrophic and weak; there was no wasting or hypertrophy of muscles in the lower limbs but the hip flexors and quadriceps were undoubtedly weak as were the oblique abdominal muscles. The deep reflexes were present, sensation was normal and the electrical excitability of the affected muscles was diminished, but there was no reaction of degeneration. At the age of 10 years the child was much improved; there was still weakness of the trapezii and of the sternal portion of the pectorales major, with slight winging of the scapulæ. The latissimi were fully restored and full abduction of the arms was possible. The boy was seen again 6 years later and seemed well and perfectly strong. In discussing this case Erb said: "I have never formerly seen recovery take place in a wide experience of such cases and did not consider it possible, but this case has taught me otherwise."

A further report of possible recovery, this time in two cases, was published by Jendrassik in 1909. The first case was a girl, the child of healthy parents; a male sibling aged 3 years was well. The child did not walk until the age of 2 years and then tended to fall frequently. At the age of 10 the gait deteriorated and on examination there was weakness of the extremities and of the abdominal and back muscles, with some flaccidity of the limbs and loss of deep reflexes. The face was not involved. Weakness in the arms was largely proximal; the small hand muscles were normal. Marked wasting of thigh muscles occurred and the patient could not rise from the floor unaided. After some six months gradual im-

provement began and progressed to complete recovery in the next four years.

Jendrassik's second case was a boy aged 12 whose uncle and sister were affected with a similar disorder. The uncle, aged 30, had developed severe weakness of the legs at the age of 8 and this was followed by loss of strength in the arms when he was 14. Weakness and wasting were progressive thereafter, wasting being particularly marked in the upper limbs and shoulder girdles; when seen he was severely disabled and showed numerous muscular contractures. The sister of the propositus, now aged 18, was in a similar condition, though she could walk (after many tenotomies) with a shuffling gait and numerous falls. The boy was three years older than his sister and the disease had begun at an earlier age; when first seen his gait was poor, his thighs were very wasted and he was unable to rise from the supine to the sitting position without using his hands. Two years later he could walk much better and could sit up easily. After another six years, the boy could walk very well and (at the age of 21 years) he had been passed for military service, although he was unable to fully extend the left knee. Although he could not be regarded as having recovered completely, the disease had certainly made no progress, unlike the condition in his sister who was now almost helpless.

The most recently reported case of apparent spontaneous recovery from myopathy was described by Bramwell (1922–3). A male child, born in 1914, was noted to have some difficulty in turning over in his cot during babyhood. There was no family history of muscular disorder. In 1917 he showed a tendency to waddle when he walked and in May 1918 he was taken to see Dr. Batten, after a diagnosis of pseudohypertrophic dystrophy had been made by another physician. Batten reported that although there was much in favour of the diagnosis of pseudohypertrophic dystrophy already given there were several unusual features which made him hesitate to give that diagnosis unreservedly. However, the child was also seen by Sir Harold Stiles who said that the gait, method of rising from the floor and laxity of the shoulder girdles were typical of pseudohypertrophic dystrophy. Professor Gulland, who saw him on the same day, concurred. During 1919 the patient began to improve and in September of that year he was seen by Bramwell, who noted slight accentuation of the lumbar lordosis, quadriceps weakness, a typically myopathic method of rising from the floor, but no localized muscular wasting or hypertrophy. There was no facial weakness. Gradual improvement continued and in March 1922 the family doctor wrote that the boy was strong and well and was in fact normal save for a residual waddling gait.

Before proceeding to discuss critically these cases of apparent spon-

taneous recovery there remain to be considered the large number of reported cases in which improvement has occurred following treatment with a variety of remedies. Hence it is unlikely that any of these reports have included cases of spontaneous recovery, unrelated to the treatment they were receiving. Great improvement occurred following cortisone or wheat-germ oil therapy in the cases of "menopausal myopathy" described by Shy and McEachern (1951), but as the authors point out the pathological changes in the muscle in this disorder are different from those in classical cases of myopathy. Denny-Brown (1952) and Adams, Denny-Brown and Pearson (1953) have given reasons for suggesting that these patients were in fact suffering from polymyositis. Recovery from thyrotoxic myopathy has, of course, been described after thyroidectomy (Sheldon and Walker, 1946) but this disorder, too, is distinct from the primary myopathies or muscular dystrophies. Great improvement was also observed as a result of treatment with wheat germ and/or vitamin E and its analogues in several of the cases of apparently typical myopathy described by Stone (1940), Bicknell (1940) and Rabinovitch, Gibson and McEachern (1951), to take three representative reports: however, complete recovery was not claimed in any case. Numerous other workers have failed to produce improvement when employing similar remedies (e.g. Fitzgerald and McArdle, 1941, Walton and Nattrass, 1954) and all evidence to date suggests that no effective treatment for myopathy has yet been discovered. In view of these facts, none of the cases described in the recent reports referred to above, and in similar papers by other authors, will be considered further in this study.

Hence there is a total of 7 cases of possible recovery to be considered, the six reviewed by Batten and that reported by Bramwell. As Batten pointed out, the case described by Levi and de Rothschild seems unlikely to have been one of typical myopathy and the same is probably true of the patient of Armand-Delille and Weil: the rapid progression of the muscular weakness makes it clear that the case was not one of typical muscular dystrophy. To turn next to Jendrassik's cases. From the information given it seems that his second case did not show complete recovery; had he done so, this would have been of fundamental importance in view of the familial incidence of the disorder. It seems, rather, that this boy had shown arrest of his disease, a phenomenon which is recognized to occur in a small proportion of cases, particularly those of the facioscapulohumeral variety. Jendrassik's first case and Marina's case are similar; both patients were girls and although the clinical findings as described favour a diagnosis of myopathy, each of them showed certain

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unusual features. To begin with, childhood dystrophy, excluding the facioscapulohumeral group, is very uncommon in girls, though by no means unknown. Secondly, the retention of the deep reflexes in Marina's case and the history of onset soon after birth with "flaccidity" in Jendrassik's case are uncommon findings. In the latter case, the possibility of congenital myopathy, as described by Aldren Turner (1940), springs to mind. Similar atypical features must have been present in the case described by Bramwell in view of Batten's hesitation in reaching a diagnosis, although it must be pointed out that two other distinguished observers regarded the case as one of myopathy. It does seem likely, therefore, that these three cases (Marina, Jendrassik—Case 1, Bramwell) recovered from a form of myopathy which was not perhaps altogether classical in its manifestations.

In the only case which remains to be considered, that described by Erb, the clinical findings as reported were characteristic of myopathy except for preservation of the deep reflexes. Batten remarked that the diagnosis in this case could hardly be called in question; however, recent experience has shown that polymyositis may give a clinical picture identical with that described by Erb in his case. This condition may simulate dystrophy so closely that without recourse to muscle biopsy the most astute clinical observer may be misled into making a wrong diagnosis.

Case 1.—A. R., male.

This patient was born at term by a normal delivery and his mother was perfectly well during pregnancy. His mother and father were healthy as were his two elder sisters and there was no history of muscular disease in the family. He walked at the age of one year and 8 months and seemed to do so quite normally. At the age of 3 he began to waddle from side to side and it was noticed that his abdomen stuck out when he walked. He tended to stumble and fall very easily and once on the floor he was unable to get up again by himself. Whereas previously he could climb stairs it was now noted that he had to pull himself up the stairs by holding the bannisters with his arms. Within a month of the onset of these symptoms his calves began to swell, particularly the right one which ached a good deal. The aching was most severe in bed at night and often woke him from sleep. The right calf was very much bigger than the left although both were swollen. I saw him at this stage and made the diagnosis of muscular dystrophy, and a month later he was seen by Dr. (the late Sir James) Spence, who confirmed the diagnosis. At that time he showed wasting of the pectorals, serrati, infra- and supraspinati, and looseness of the shoulder girdles. There were marked lordosis with characteristic "climbing up the legs," the thigh muscles were weak and those of the calves were hypertrophied. Within a year the condition had progressed so much that he was unable to walk more than a few yards by himself and had to be carried to school. At this time treatment with nicotinic acid, 100 mg. t.d.s. was begun by his doctor. The condition remained relatively stationary for another three months or so and then began to improve. He became able to walk longer distances, fell less frequently, and climbed stairs with much less effort.

Constant encouragement on the part of the parents was a feature of his management. At the age of 6 he was able to run in races at school. Gradual improvement continued and by the age of 6½ no swelling of the calves was evident. At the age of 8 he seemed completely normal. Now at the age of 11 he lives a perfectly normal life, plays rugby football and does "gym" at school though it is perhaps true that he cannot run as quickly as many boys of his own age. At no stage during the illness was there any thickening or inflammation of the skin although the calves when swollen were always tender. There was no difficulty in swallowing, no weakness of the neck, no hypotonia and no Raynaud's phenomenon. It was, however, noted that the muscles of the thighs and calves and shoulders seemed very stiff at the height of the illness.

On examination on March 3, 1952, he was a healthy-looking boy who walked and ran perfectly well and rose from the floor without difficulty. There was no muscular wasting or weakness on detailed examination and no neurological signs could be demonstrated. The skin was perfectly normal and showed no evidence of thickening or scleroderma.

Comment.—There can be little doubt of the diagnosis of muscular disease. The only atypical features were, firstly, the tenderness of the calves, and, secondly, the rapid progression of the disease. However, pain in muscles showing pseudohypertrophy is not infrequent in classical myopathy, and there was certainly no evidence of involvement of skin and bulbar muscles as would have been expected if the case were one of typical dermatomyositis. Pseudohypertrophy of muscle is very uncommon in any condition other than muscular dystrophy: but it has been described by Tyler (1950) in cases of periodic paralysis and has recently been observed in cases of proved polymyositis. It is very uncommon for myopathy to progress so rapidly that the patient is practically unable to walk within a year of the onset, and it seems that this relatively acute course is the most important atypical feature. It is very unlikely that the drug therapy employed was responsible for recovery; it is, however, worth stressing the continual optimistic attitude of the parents. Speculation as to the effect of such psychological factors would probably be fruitless, although it is of interest that a similar approach was employed by the parents in several of the other cases which are to be described.

Case 2.—A. W., male.

This boy was born at term by a normal delivery and was perfectly well in the first three years of life. He walked shortly after the age of 1 year and seemed quite normal and active. There was no family history of muscular or neurological disease; his father and mother and sister (now aged 18) were well and have remained so since. In 1944, at the age of 3, he developed a disinclination to play with boys of his own age because he was unable to keep up with them. He was inclined to play on the floor and it took considerable persuasion to make him get up again. Soon afterwards he became unable to do so except with considerable effort. He walked stiffly with his trunk bent backwards and seemed to push each hip forward one at a time as if he were pushing himself along. At about the same time it was noted that when he picked up a cup he used both hands and sometimes in lifting objects he would put one hand under the other elbow in order to lift it. Within three months he was unable to walk more than 50 yards, could not get

up from the floor without assistance and was unable to climb a step 6 in. high. Shortly afterwards he developed chicken-pox and was in bed a fortnight; when he got out of bed he was very much worse and could hardly walk at all. At this time it was noted that there was marked wasting of his shoulders and of the upper part of his arms and of his thighs. Despite this the calf muscles were very large and swollen.

During the first year of his illness the boy was taken to see Dr. (now Sir) Russell Brain who recorded that "he walked with a waddling gait and there was considerable lumbar lordosis. There was weakness and wasting of shoulder girdle muscles and pseudohypertrophy of the hamstrings and calf mucles. He was unable to rise from the ground without help. There was weakness of flexion of the trunk and extension of the hips. The tendon reflexes in the upper limbs were present, the knee and ankle jerks were absent and the plantar reflexes were flexor." A diagnosis of pseudohypertrophic muscular dystrophy was made.

The patient was seen shortly afterwards by Dr. C. N. Armstrong and was given 1 oz. of Bemax per day. Within two or three weeks there was very considerable improvement. One day the mother went into the bedroom and found the boy sitting up by himself; before that time he had to be turned over in bed and had never attempted to sit up though he was able to lift his head off the pillow. Improvement has since been gradual but steady. He began to ride a tricycle and was able to ride up slopes which he had never tackled before. At the end of twelve months he was able to walk half a mile or more, and six months later he walked upstairs easily. He also became able to get up from the floor normally.

Gradual improvement has continued and now, although he cannot run very fast, he lives a perfectly normal life and plays football and cricket. He has been able to do physical training at school without any difficulty.

He took Bemax in 1944 for six months but then later was taken to see Dr. Franklin Bicknell who altered the treatment to 3 capsules of Vitamin E (each of 6 mg.) per day. Later, 3 yeast tablets daily were added and this treatment has been continued up to the present time.

At no time was there any weakness of the neck or skin rash, there was no dysphagia, no Raynaud's phenomenon and no pain or tenderness of muscles, nor was there any clear fatiguability. Improvement first took place in the legs, but the power of the arms has returned much more slowly over the years.

The patient was re-examined by Dr. Russell Brain on March 14, 1950. He noted that "the scapular muscles were small and the deltoids somewhat wasted. The deltoids and rhomboids were weak and the triceps slightly weak but the upper limbs were otherwise normal. The flexors of the trunk were somewhat weak and there was slight weakness of both quadriceps. There was no pseudohypertrophy and all the tendon reflexes were present and the plantars flexor. On rising from the lying posture he has slight difficulty to start with owing to weakness of flexion of the trunk, but thereafter he gets up without great difficulty and he no longer helps himself up with his hands.

"It is thus clear that this boy is very much better than he was when I first saw him nearly six years ago. I have considered the possibility that the original diagnosis might have been wrong, but no alternative seems at all probable. His condition in 1944, apart from the rather rapid onset and his age, was typical of pseudohypertrophic dystrophy and his present condition is unlike the sequel of any recognizable nervous disorder of acute onset, but is quite consistent with a pseudohypertrophic muscular dystrophy which has for some reason considerably regressed."

Examined in November, 1951, the boy was healthy, agile and active. His gait was normal, he ran briskly and rose from the floor normally. On detailed examination there was very slight residual weakness and wasting of the serrati, rhomboids, pectorals and quadriceps but all other muscles appeared normal. The skin showed

no abnormality and there were no abnormal physical signs in the central nervous system or any other system.

Comment.—As with Case 1, the detailed clinical information available concerning this patient makes any other diagnosis than one of muscular disease very unlikely despite the absence of pathological confirmation. Although very slight residua of his illness remain, for all practical purposes he can be regarded as having recovered completely, and his father writes (in June 1953) that the boy has continued to improve and is now well and strong. Again, the only atypical feature in this case was the rapidity of progression of the disease. The marked improvement beginning after the administration of Bemax is of great interest; it should be pointed out, however, that this remedy has been utilized in many cases of classical myopathy without effect. It must be suggested therefore, either that this was a spontaneous recovery unrelated to treatment, or that the changes in the muscles in this case were different from those in classical myopathy and showed response to wheat-germ therapy. With this patient, as with Case 1, psychological factors may have played a part; his father and his mother (a trained nurse) surrounded him with an aura of optimism and continual encouragement.

Case 3—A. A., male.

This boy, a full-term, normal baby, was perfectly well until the age of 7. There was no family history of muscular or neurological disease. The patient's elder brother, now aged 22, is healthy. The patient went regularly to school, played games well and could run and jump as well as the other children. He then had an attack of scarlet fever (March 1940) and on getting out of bed he walked badly. He was awkward and would fall easily, appearing to trip over anything; when he got down on the floor he was comp'etely unable to get up again and soon, indeed, it was noted that if he fell on his back he could not roll over. If he fell forward he would get on to his hands and knees but could never get any farther. He became unable to climb up stairs except by crawling and within two months was unable to walk across the room. At the same time he began to gain a great deal of weight. He was taken to see an orthopædic surgeon at Cosham Hospital, Bristol, who diagnosed muscular dystrophy.

Within a few weeks the weakness and difficulty in walking were so bad that the boy became confined to a wheel-chair and had to be carried upstairs. His arms became so weak that he could only just lift a spoon to his mouth.

He was taken to see Mr. H. Chitty at the Central Health Clinic, Bristol, and the diagnosis of muscular dystrophy was confirmed. Unfortunately the record of his original attendance has been lost but, writing in December, 1951, Mr. Chitty said "I do not care to trust my memory for exact details as to his condition when first I saw him, or for the history of onset of the disease. I do know, however, that he had extensive wasting and weakness of scapular muscles and enlargement of the calves and that when first seen he could only get up when supine by climbing up his own legs in the typical pseudohypertrophic fashion. I also recollect that his steady improvement, which did not begin until I had had him under observation for a considerable time, made me doubtful of the original diagnosis of which I had previously been confident, regarding him as a typical case."

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The patient's mother was a trained nurse and fully understoood the gravity of the prognosis of muscular dystrophy. Both parents therefore decided that they must keep the child on his feet as long as possible. They compelled him to walk and would not help him unless it was absolutely necessary. They noted that if he was allowed to stay in bed the weakness became very much worse and so they continually kept him occupied, made him move about and were always cheerful and optimistic.

For eighteen months the boy remained severely disabled and deteriorated further. Then his mother learned from a sister in America that Tocophorex (Squibb) and Combex (Parke, Davis) had been used with some success on cases of muscular dystrophy. She obtained these drugs from America and gave the boy one capsule of each twice a day. Almost immediately gradual improvement was noted. One day he was seen to pick up a knife and cut a potato; gradually he began to walk upstairs and the pronounced waddle which had been noticed in his gait disappeared. The Tocophorex was given for eighteen months. Mr. Chitty recorded on February 27, 1942, that muscular power was greatly improved and the calves looked more normal. On February 5, 1943, the arm and shoulder muscles appeared normal and he could get up from the floor without "climbing up his legs," although he got rather tired after walking a mile. On May 24, 1945, he saw Mr. Chitty for the last time and was now aged 13½ years. He appeared to have recovered completely and showed no evidence of muscular wasting or weakness. Thus recovery seemed to be complete five years after the diagnosis was made and the boy has been well since. He has played games regularly, has been strong for his age and has lived a completely normal life. At the height of his illness he tended to lean backwards and walked with a waddling gait but for the last ten years he has walked perfectly normally.

During the illness the muscles of the shoulders and thighs became very thin indeed but despite this he gained a good deal of weight and his skin looked tight and waterlogged. However, there was no weakness of the neck nor Raynaud's phenomenon and he had no difficulty in swallowing, nor was there any pain or tenderness in the muscles. Although the skin over the trunk looked tight, that on the hands appeared to be normal and was never inflamed or shiny. The calves looked large and shapeless throughout the illness in striking contrast to the thin thighs but this, too, gradually disappeared as he got better.

The patient was examined on November 28, 1951, while serving in the Army as a private in the Royal Army Pay Corps. He remembered very little about his illness and could add nothing to the history given by his mother.

On detailed physical examination there was no muscle wasting or weakness and no hypotonia. All muscle groups were of normal power and there were no abnormal signs in the central nervous system. The skin was normal thoughout and all other systems showed no abnormality.

Comment.—The clinical history in this case shows striking similarity to that in Cases 1 and 2. From the information available, primary muscle disease seems to be the only possible diagnosis but once more the rate of progression of the disease was much greater than that commonly observed in muscular dystrophy. Improvement began shortly after the administration of a preparation of mixed natural tocopherols but it is impossible to be sure whether this treatment was responsible. The psychological approach of the parents to the problem is again worth noting.

Case 4.—R. L., male.

This boy, a full-term, normal baby was well until the age of 11. His mother, father, two elder brothers and elder sister were healthy and remained so, but a male cousin was said to have died at the age of 15 years from progressive muscular dystrophy. The latter child was taken to the Derbyshire Royal Infirmary at the age of 8 years, having had difficulty in walking for two or three years. His mother was told that nothing could be done for him and that he would become progressively weaker. This did, in fact, occur; the boy became confined to a wheel-chair and eventually died at the age of 15. Although the relatives say he was diagnosed as a case of muscular dystrophy it is unfortunate that no medical records have been traced.

The patient concerned in the present report was very athletic and at the age of 10 could jump 4 feet in the high jump. One day at the age of 11 when he was playing cricket, his father, who was watching, noticed that he did not seem to run properly, and seemed to bend his trunk forward, as if he were having to push himself along. A day or two later his mother noticed when he was walking home that he seemed to waddle and each side of his pelvis seemed to go forward alternately as he walked. Gradually, over five or six weeks, these signs increased, he had increasing difficulty in running and also seemed unable to climb stairs or to get out of a low chair without a struggle.

The boy was taken to his family doctor who at first could find nothing wrong but later noticed that he was unable to rise from the floor. He was referred to Mr. Ratcliffe in the Orthopædic Department of the Derbyshire Royal Infirmary who diagnosed muscular dystrophy and prescribed seven injections of "Pregnyl" (chorionic gonadotrophin) at weekly intervals.

At first there was no change in his condition but after he had had the sixth injection he began to improve. Within a few weeks he was completely normal again and played games vigorously for the next two years without any evidence of weakness. However, at the end of this period he again began to have difficulty in getting out of chairs and in rising from the floor. Over the course of a few weeks he steadily became worse. At first his arms were unaffected but later he could not lift them above his shoulders. Eventually walking became extremely laboured, he seemed to lean forward like an old man and lifted each leg laboriously. By this time the muscles of the shoulder and of the thighs were very wasted but there was no enlargement of the calves or of any other muscles. Slow, steady deterioration continued for twelve months; during this period he was constantly reassured by his family and was encouraged to walk even when he was almost unable to do so.

Towards the end of this year of deterioration he was given two more courses of "Pregnyl" injections with no significant change. It was then noted that for a period of a few weeks the disease seemed to be stationary and soon afterwards slight signs of improvement began. He discarded his wheel-chair and began to walk more easily and soon was able to climb stairs, though with difficulty.

In 1944, eighteen months after the onset of the second episode, he was taken to the West End Hospital for Nervous Diseases under the care of Dr. L. R. Yealland. On admission to hospital, some wasting of the latissimus dorsi and of the clavicular portion of the pectorals was noted. The erector spinæ were weak, as were the quadriceps and hip flexors. All tendon reflexes were present though sluggish. Dr. Yealland felt that the diagnosis must be one of muscular dystrophy even though some improvement was noted in the boy's condition during his month's stay in hospital.

On discharge from hospital he was given another course of "Pregnyl" injections and from that time appeared to improve steadily once more. On this occasion improvement was rapid; within six months all evidence of muscular wasting and weakness had disappeared. He has been perfectly well ever since and now, at the

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age of 22, he plays in tennis competitions. His mother, a trained nurse, stresses the psychological element; she insists that he always believed he would recover and that with the repeated encouragement from his family he always worked toward that goal.

Apart from muscular weakness there were no other symptoms during this illness. There was never any weakness of the neck muscles nor was there any systemic upset or pyrexia. The skin of the fingers and hands was not involved, there was no Raynaud phenomenon and no difficulty in swallowing. The muscles were never tender or painful. It was, however, noted that at the height of the complaint the muscles were fatigable; they were always made weaker by exercise and improved after rest and the boy seemed stronger in the mornings. He was never able to carry out an action as well after attempting it two or three times.

Examination on February 27, 1951, revealed a well-built, well-developed youth, 6 ft. 1 in. in height and athletic and nimble in all his movements. On detailed physical examination no muscular weakness, wasting or hypotonia was evident. The skin was normal throughout and there were no abnormal physical signs in the C.N.S. or, indeed, in any other system.

Comment.—The family history is of considerable importance in this case. It is well recognized that the childhood (Duchenne) form of muscular dystrophy is commonly transmitted as a sex-linked recessive factor. This has been confirmed in a study of 48 typical cases, which showed that this form of the disease may sometimes begin later than in the first decade (Walton and Nattrass, 1954). Hence if R. L. were to be regarded as a typical case of this affection, the appearance of pseudohypertrophic dystrophy in a male maternal cousin is in conformity with the accepted pattern of inheritance. However, although the distribution of muscular weakness and wasting in R. L. certainly favoured a myopathy as the most likely diagnosis, it must be admitted that even more than in Cases 1, 2 and 3, there were certain very atypical features. Fatigability, which seems to have been a feature of the illness, though not to a marked degree, is uncommon in typical myopathy, while cases of the latter type usually walk leaning backwards with an accentuated lumbar lordosis, not leaning forward as did R. L. Rapid progression of disability was again noted in this case, while the remittent course, with two distinct episodes of weakness, is even more unusual. However, fatigability of muscle and a remittent course are both typical features of polymyositis. It seems very unlikely that "Pregnyl" injections could have been responsible for improvement as they were given at the height of the second episode without apparent effect. It is a remarkable coincidence that R. L.'s mother was also a trained nurse and she felt confident that continual encouragement and optimism played a part in her son's recovery.

Case 5.—V. C., female.

This patient was born at term by a normal delivery and her mother was healthy during pregnancy. There was no history of muscular or neurological disease in the family and five siblings are normal. The patient walked normally at the age of 10

months. One day, at the age of 2½ years, she went into the sea to bathe; the water was very cold at the time. On coming out of the water, her mother noticed that she seemed to be dragging the left leg. The next day she seemed to waddle from side to side when she walked and within a few days she began to walk rather stiffly with a protruding abdomen. Within a week she began to fall a great deal, and once on the floor she could not get up again. If she was lying on her back she would roll over, crawl to a table leg and pull herself up. Soon afterwards she became unable to sit on a chair and would fall off if not supported. Over a period of two months she deteriorated steadily and was eventually admitted to the Fleming Memorial Hospital for Children, Newcastle upon Tyne. She was in bed in hospital for two weeks and a diagnosis of muscular dystrophy was made. Unfortunately the record of clinical findings has been mislaid. On discharge from hospital she could not walk and was unable even to stand by herself. A week later she was able to walk a few steps with help. Her mother constantly encouraged her, insisting that she should not be carried and should be made to walk whenever possible. Two weeks after discharge from hospital she was seen by Dr. C. N. Armstrong who found weakness and wasting of shoulder and pelvic girdle muscles and made a diagnosis of muscular dystrophy; he advised treatment with Bemax. Immediately after this remedy was begun the patient began to improve; there was an initial rapid improvement so that within a week or two she was able to walk a few hundred yards and could get up a number of stairs by herself. However, after this time improvement became much slower and at the age of 6 she was still walking with a slow waddle and a protuberant abdomen. Between the ages of seven and eight her posture seemed to correct spontaneously and she became able to run as fast as other children and to play games without any disability. Ever since that time she has lived a perfectly normal life with no evidence of muscular abnormality.

At no time was there any drooping of the eyelids, weakness of the neck, alteration in speech or difficulty in swallowing. The muscles were never tender nor had she suffered from the Raynaud phenomena and there were never any obvious changes in the skin.

On examination in September 1951 the patient was a healthy-looking, intelligent girl who walked briskly with no noticeable abnormality of gait. She rose normally from the floor without using her hands and sat up briskly from the supine position. Detailed examination of the muscular system revealed no wasting or fasciculation; there was perhaps very slight weakness of the triceps in the upper limbs and of quadriceps in the lower limbs but this was minimal. All tendon reflexes were present and equal and the plantar responses were flexor. There was no skeletal deformity and examination of other systems revealed no abnormality. An electromyogram taken from the right quadriceps muscle was entirely normal.

Comment.—The mother's description of this child's condition at the height of her illness and Dr. Armstrong's clinical records leave little doubt that this patient showed muscular wasting and weakness of typically myopathic distribution. Once again the only atypical feature was the rapidity of onset and progression of the disease. In this case the onset appeared to have been even more acute than in Cases 1 to 4, although it must be admitted that rapid deterioration after trauma or bed-rest is sometimes seen even in classical myopathy, and it is possible that minimal but unrecognized weakness was present before the child went bathing. The fact that improvement began immediately after the administration of

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whole wheat germ is of interest and should be compared with the findings in Cases 2 and 3.

Case 6.—S. B., female.

This patient, a full-term normal baby, was quite normal until she was aged 7 years 9 months. Her mother, father and elder brother and sister were quite well and have remained so, although her sister's fingers have tended to go cold and white during cold weather for some years. Following an attack of measles she was away from school for six weeks. On returning to school it was found that she could not run as well as the other children, she was slow and fell a great deal, seeming to trip very easily. Three months later she had chicken-pox and the weakness increased further. On getting out of bed she was unable to walk upstairs, she walked with a waddle and a protruding abdomen and soon afterwards began to walk on her toes. She was unable to get up from the ground without using her hands and could not lift heavy weights. In addition her neck was weak and she could not lift her head from the pillow. There was also some difficulty in chewing and soon afterwards she found difficulty in swallowing solid food though she could manage liquids perfectly well. However, this latter symptom was transient and relatively mild and was only brought to light by direct questioning.

The condition seemed to improve towards the end of the day as she got loosened up but at other times her muscles seemed to be stiff. This stiffness was not affected by the weather although at about the same time her fingers began to go white and dead whenever it was cold.

There was no muscular tenderness at any time, but the stiffness seemed to become particularly severe when she went to bed at night. There was never any noticeable change in the skin of the hands, face or elsewhere.

At this time she was seen by Dr. J. C. Spence who noted that the child walked with a waddling gait and an accentuated lumbar lordosis; she could not climb stairs or rise from the floor and a diagnosis of myopathy seemed incontrovertible. He suggested empirical treatment with Livogen. The patient's condition seemed to remain stationary for about 6–9 months. She was seen again by Dr. Spence who saw no reason to doubt his original diagnosis. Shortly afterwards, however, she began to improve and improvement was progressive, though slow, thereafter. Five years later, at the age of 13, she appeared to have recovered completely, although she continued to take Livogen for another five years. She was seen again by Dr. Spence in 1947 and he confirmed that she had recovered completely.

On October 15, 1951, at the age of 23, she was a healthy-looking girl who walked briskly with no abnormality of gait. Detailed examination of the muscular system revealed no abnormality, save perhaps for a slight bilateral weakness of quadriceps. There was also a slight dorsal scoliosis convex to the left side but there was no accentuation of the lumbar lordosis. The skin was normal showing no evidence of scleroderma; all tendon reflexes were active and equal.

Comment.—Although the history of weakness in the muscles of the pelvic girdle in this case was very similar to that obtained from cases of classical muscular dystrophy, there were several features which, in retrospect, must make the diagnosis questionable. Once again the rate of progression of the disease was much greater than that usually experienced in typical myopathy, but in addition the weakness of the anterior neck muscles, the dysphagia, the Raynaud phenomenon and muscular stiffness are not, as a rule, a part of the clinical picture of muscular dystrophy.

While it is true that the Raynaud phenomenon may have been unrelated to the primary disease (the patient's sister also suffered from coldness and pallor of the fingers), it should be pointed out that the patient has not experienced this symptom since recovery from her muscular disorder. All of these atypical features, together with weakness of pelvic and shoulder girdle musculature, have been observed by Walton and myself in 3 cases of dermatomyositis in childhood, 2 of which were referred as cases of muscular dystrophy by consultant physicians. In the latter 2 cases, as in S. B., symptoms such as dysphagia, weakness of neck muscles and the Raynaud phenomenon were only brought to light by direct questioning, while no complaint was made concerning the skin; it was only on careful examination that minimal scleroderma-like changes were observed in the skin of the hands and face. In the third case, skin changes were much more obvious and extensive and are progressing, whereas the other two patients are both showing considerable spontaneous improvement. It seems probable, therefore, that S. B. was suffering from dermatomyositis with minimal skin involvement or perhaps none at all, and that she has made a spontaneous recovery from this condition.

Case 7.—J. W., female.

This patient was born at term by a normal delivery and the course of her mother's pregnancy was normal. Shortly after birth her mother thought that the child's legs looked too thin but no one else agreed with her. She walked at 10½ months but soon afterwards it was noted that she walked with a waddle and her abdomen protruded. She continued to walk in this way and at the age of 2 years it was seen that she could not walk upstairs except by pulling herself up with her arms. At this age her mother was quite certain that the thighs and calves were abnormally thin. The patient tended to fall very frequently, seeming to trip over non-existent obstacles. If she rolled over on to her back she could not roll over by herself and if she fell to the floor she could only get up with a great struggle and by climbing up her legs. The condition did not get worse and, indeed, seemed to be at a standstill for many years. At no time was there any "floppiness" of the limbs or other evidence of hypotonia. The child was taken to see Dr. J. C. Spence in 1943 at the age of 8 and was admitted to the Royal Victoria Infirmary for observation. On examination she was a rather obese child; when she stood there was accentuation of the lumbar lordosis and the abdomen protruded. She walked with a waddling gait and rose from the floor by climbing up her legs; she was unable to rise from the supine to the sitting position without using her hands. There was no evident muscular wasting although the legs below the knee were somewhat thin when compared with the thighs. There was no winging of the scapulae but flexion of both arms was weak; the lower limbs showed weakness of hip flexion and of the quadriceps bilaterally. Dr. Spence felt that the condition was most likely to be a progressive muscular dystrophy despite the atypical features.

At the age of 10 or 11, the patient began to feel stronger. From that time she has improved steadily, though very slowly. When seen at the age of 16 (December 1951) she was able to walk for miles, and could run upstairs. At no stage was there any weakness of the arms or of the neck muscles and speech was never affected. She suffered at no time from Raynaud's phenomenon nor was the skin in any way

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abnormal. It was, however, noted that ever since birth both eyelids had tended to droop, though this had not varied. She had always had stubby fingers and webbed feet. Her mother, too, had webbed feet, as had two female siblings and there was a history of this anomaly in her maternal great-grandmother. There was no history of muscular disease in the family.

On examination in December 1951 the patient was cheerful, co-operative and intelligent. She walked with a slightly accentuated lumbar lordosis and a slight waddle. She could get up from the floor without using her hands but had considerable difficulty in sitting up from the supine position. There was distinct bilateral ptosis of moderate degree but ocular movements were full. There was no abnormality of the shoulders or wasting of shoulder girdle or arm muscles nor was there any muscular wasting or fasciculation in the lower limbs. No hypotonia was evident.

On detailed examination of the muscular system there was slight weakness of the iliopsoas, gluteus maximus, quadriceps and the adductors of the thigh bilaterally but all other muscles seemed to be of normal power. The hands were stubby and curiously misshapen, the proximal phalanges being broad and long, the terminal ones short and narrow. The second and fifth fingers had no terminal interphalangeal joints. There was moderate bilateral pes cavus, and the middle three toes of both feet were webbed, the great toe being unusually large. Other systems showed no abnormality.

An electromyogram on June 25, 1952, from the right quadriceps showed no spontaneous activity. A normal interference pattern was obtained on volition while recording from most parts of the muscle, but superficially a high proportion of polyphasic potentials were obtained, and analysis with the audio-frequency spectrometer (Walton, 1952) showed a complete shift to the right. These appearances were characteristic of primary muscle disease. The electromyogram from the right tibialis anterior and the right gluteus maximus was normal. Muscle biopsy (June 26, 1952) from the right quadriceps showed that the muscle bundles were largely of equal thickness. Occasional atrophied muscle fibres were seen. No significant proliferation of sarcolemmal nuclei was seen. There appeared, however, to be present an increase of fatty tissue which was penetrating between the muscle bundles and apparently replacing the atrophied muscle fibres. The picture was not unlike that seen in pseudohypertrophic muscular dystrophy (Dr. R. Schade).

The patient was seen again on December 19, 1953, and showed further improvement, being able to sit up with much less difficulty. Weakness of the muscles of the pelvic girdle was much less evident.

Comment.—The onset of muscular weakness in this case was at an earlier age than is usual in progressive muscular dystrophy, although in some of our 48 cases of typical childhood dystrophy there was some clinical evidence of muscular abnormality in the first year of life. The early onset of the disorder with subsequent improvement must make one consider a diagnosis of amyotonia congenita, but the absence of any muscular hypotonia, combined with the fact that the child walked at an early age, is very much against this diagnosis. Furthermore, Brandt (1948) has shown clearly that amyotonia congenita is a symptom of a variety of neuromuscular disorders and not a single disease; most children in whom this diagnosis is made turn out to be suffering from progressive infantile spinal muscular atrophy (Werdnig-Hoffmann) and show steady progression of the

disorder. However, Aldren Turner (1940 and 1949) has defined another group of cases falling within the boundaries of the symptom-complex of amyotonia congenita. His patients appeared to be suffering from a congenital non-progressive myopathy and he called them the myopathic type of amyotonia congenita to distinguish them from the spinal type (Brandt). The electromyographic and biopsy findings in M. W. certainly favoured a myopathic degeneration but she did not show the typical picture of amyotonia in infancy, and since she walked at the normal age there is no evidence that her condition was congenital. Furthermore, Aldren Turner's cases, though showing no progression of muscular weakness, did not recover as M. W. appears to have done. Despite these discrepancies, it seems most likely that this patient was suffering from a benign congenital myopathy. Certainly there was no evidence of the slow inexorable deterioration seen in classical myopathy or of rapid progression of the disease as observed in Cases 1 to 5.

Case 8.—A. T., female.

This patient was born at term by a normal delivery and her mother was healthy during pregnancy. Her mother and father and five siblings were healthy and have remained so. She seemed to be a beautiful baby and behaved quite normally at first. She sat up at the normal age but at 12 months made no attempt to walk; she could stand but soon fell down and propelled herself round the floor by shuffling on her bottom. She seemed to have some weakness of both legs which dragged considerably when she tried to walk round the furniture. Further, she did not stand as a normal child would; her head, neck and shoulders seemed to be hunched and her abdomen was protuberant. At the age of 2 years she began to walk by herself but constantly fell down; her legs seemed to give way and once on the floor she could only get up by climbing up her legs. For several years she was quite unable to climb stairs unaided. She walked little and with a waddle, seeming to swing her legs laterally. It was also noted that her arms were weak and she could not lift food to her mouth properly except by lifting one arm with the other. She also had some difficulty in swallowing, particularly solid food, from an early age; no drooping of the eyelids was noted nor was there any alteration in her speech. From the beginning her legs seemed to be loose and "floppy" and could be put into very unusual positions; her legs could almost be tied around her neck and on being lifted up she seemed to slip through her mother's hands. There was no pain, tenderness of muscles or Raynaud phenomenon.

At the age of five, a physician was consulted and the mother was told that she was a case of muscular dystrophy. Unfortunately the clinical record of this consultation cannot be traced. At the age of 6 she was taken to see Dr. W. G. Wyllie at the Hospital for Sick Children, Great Ormond Street. According to the available records she then showed marked lordosis and a waddling gait. The glutei were well developed, the calves were wasted, right more than left, and the knee-jerks were present on reinforcement only. Dr. Wyllie felt that she was a mild case of amyotonia congenita. From this time until the age of 10 the patient showed no significant change. Since then improvement has been steady. She can now walk, run and climb stairs and cycles four miles to school every day.

On examination on October 5, 1952, she was a healthy-looking, active, cheerful girl who walked with an athletic gait with no waddle and no increase

in the lumbar lordosis. She got up from the floor and out of low chairs without using her hands and sat up from the supine position in a perfectly normal fashion. There was slight bilateral ptosis but no weakness of the face or palate. The other cranial nerves were normal; no abnormality was noted in the skin. In the upper limbs there was slight reduction in power of the deltoids and triceps in both arms but all other muscles were normal though the tendon reflexes were depressed; the abdominal reflexes were present. In the lower limbs both iliopsoas muscles were a little weak, particularly on the left side as were the adductors and quadriceps. There was some hypotonia of these muscles, again more on the left. All muscles below the knee were normal in power. All tendon reflexes in the lower limbs were absent and both plantar responses were flexor. There were no other abnormal signs in the central nervous system or elsewhere.

Comment.—The history of generalized muscular hypotonia and weakness of early onset, combined with dysphagia, clearly indicates that the patient was not suffering from progressive muscular dystrophy. These features bring to mind at once the symptom-complex of amyotonia congenita. It seems improbable that this girl was suffering from the spinal type of amyotonia since Brandt (1948) has shown that most cases so designated show progressive disability and he believes that they are, in fact, cases of the Werdnig-Hoffmann disease. It is, of course, possible to postulate that anterior horn cell damage was maximal at birth and did not extend subsequently, a view expressed by Grinker (1927), but this concept of the disease has not been confirmed. Furthermore, this would certainly not explain the improvement which began at the age of 10 years; indeed this latter feature of the natural history of the illness does not lend itself to any ready explanation. It must, however, be agreed, that as in Case 7, the progress of the disorder was compatible with a diagnosis of benign congenital myopathy. Despite the absence of pathological evidence, such a condition would appear to be the most probable explanation of this patient's illness.

Discussion

An assertion to the effect that recovery has occurred in patients suffering from a disease which is regarded as incurable demands very careful consideration before the evidence can be regarded as conclusive. In the review of the literature it was pointed out that only one such case, that described by Erb, appeared to be suffering from a typical myopathy. At least one other showed arrest of his disease but not recovery, while all the remainder showed atypical features sufficient to cast doubt upon the diagnosis or at least to suggest that they were suffering from a form of myopathy which was different from the classical type. It is also true that in these reported cases there was no single distinctive atypical feature or group of features sufficient to help in defining a myopathic syndrome in which recovery is the rule. On the other hand, the absence of such a

common denominator in information gleaned from published reports does not necessarily mean that points of similarity were not present, since different observers tend to describe cases in different ways, some stressing one particular clinical feature, others another. Hence it is possible even in Erb's case, that if the patient had been interviewed and examined by a number of physicians, atypical features might have come to light which were not described in Erb's communication. The most that can be said then, with regard to published reports, is that spontaneous recovery appeared to have taken place in one case of myopathy which seemed to be clinically typical and in at least 3 atypical cases.

To turn to our cases, it must be said at once that Cases 7 and 8 were sufficiently atypical to raise doubts in the minds of the original observers as to the accuracy of the diagnosis of progressive muscular dystrophy. Both cases, particularly Case 8, showed some resemblance to the symptom-complex of amyotonia congenita. In retrospect it seems likely that these patients were suffering from a form of benign congenital myopathy. In Case 6, too, the weight of evidence suggests that the diagnosis of progressive muscular dystrophy was wrong. It is not generally recognized that dermatomyositis may present with signs of muscular weakness in the pelvic and shoulder girdle and that skin changes may be minimal. The presence of certain mild symptoms in Case 6 which were not stressed by the parents (dysphagia, Raynaud phenomenon, weakness of anterior neck muscles) suggests that dermatomyositis may have been the cause of her disability.

In the remaining 5 cases, the clinical histories and the recorded observations of numerous experienced physicians suggest there can hardly be any alternative to a diagnosis of primary muscle disease. In Case 4 the fatiguability, the unusual posture and the remittent course of the illness and in Case 5 the remarkably acute onset make it very unlikely that either patient was suffering from classical progressive muscular dystrophy despite the family history in Case 4. In Cases 1, 2 and 3, however, the clinical picture appeared characteristic of pseudohypertrophic muscular dystrophy, even including the typical enlargement of the calves; the only unusual feature in these three cases was the rapid initial progress of the disease, a point also noted in Cases 4 and 5.

It is important to consider the possible effect of treatment in these cases. Case 1 received empirical therapy with nicotinic acid, Case 4 with "Pregnyl" (chorionic gonadotrophin) but in neither case did the beginning of improvement appear to be related to the administration of these remedies and it is difficult to see what effect either could have had upon the muscular disorder. It is probably justifiable to assume that in both of

these cases recovery was spontaneous and unrelated to treatment. The other three cases, however, all began to improve shortly after treatment with wheat germ (Bemax in two cases, mixed natural tocopherols in the other) was begun. In all three patients improvement began so soon after the beginning of therapy that it is difficult to escape the conclusion that there may have been some relationship between the two events. This possibility brings to mind the therapeutic effects with wheat germ or cortisone achieved in cases of "menopausal muscular dystrophy" by Shy and McEachern (1951). As already mentioned, the pathological changes in the muscles of the menopausal cases are entirely different from those observed in classical muscular dystrophy. The muscle shows patchy necrosis of muscle fibres and active phagocytosis of sarcoplasmatic remnants, cellular infiltration, and often evidence of regeneration. In addition, rapid progression of muscular weakness and a tendency to remissions is observed in this disease. As Denny-Brown (1952) and Adams, Denny-Brown and Pearson (1953) have observed, these clinical and pathological findings are identical with those seen in dermatomyositis save for the absence of skin involvement. Within recent years it has become evident that cases of this type are not confined to the menopausal age group and that they may occur in childhood, when the clinical resemblance to muscular dystrophy may be extremely close. Adams (1954), Walton (1954) and I myself have lately observed such cases in the acute stage. These patients were all regarded as examples of muscular dystrophy until muscle biopsy revealed the characteristic features of polymyositis. Eaton (1954) has had a similar experience. Several of the patients seen by these workers recovered spontaneously; others responded to treatment with cortisone or ACTH.

It now seems very probable that Cases 1—6 were not the subjects of a primary myopathy but that most, if not all, were suffering from polymyositis; and furthermore that this disease explains the great majority of published reports of recovery from "muscular dystrophy." Clearly this experience must indicate the paramount importance of muscle biopsy in the investigation of cases of this type. This procedure is indicated in any patient suffering from proximal muscle weakness which is unduly rapid in its progression or in any atypical case, as the prognosis of polymyositis is very different from that of classical muscle dystrophy and effective treatment may be possible.

Summary

The muscular dystrophies are generally regarded as incurable diseases, but a number of reports have appeared of recovery in isolated cases believed

to be of this nature. A review of the literature has revealed descriptions of spontaneous recovery in one apparently typical case and in three cases showing atypical features. None of the recent papers claiming benefit from a variety of therapeutic regimes contains any well-documented case of complete recovery.

Eight cases are reported, all of whom had recovered, either completely or almost completely, from a condition previously diagnosed by experienced observers as progressive muscular dystrophy. Reasons are given for supposing that two of these patients may have been suffering from a benign congenital myopathy and another from dermatomyositis. In the remaining 5 cases the clinical findings were characteristic of the childhood or Duchenne type of muscular dystrophy save for the facts that one patient suffered two separate and distinct episodes of muscular weakness and that in all 5 cases the onset of the disease was much more rapid than is usually the case in classical progressive myopathy. In two of these cases recovery was probably spontaneous but in the others improvement appeared to be related to the administration of wheat-germ preparations.

Evidence is advanced that these 5 patients were suffering from polymyositis, a condition similar both ætiologically and pathologically to dermatomyositis save for the absence of skin involvement. Rapid progression of muscular weakness and a tendency to spontaneous remission are two features which may serve to distinguish this group of cases from those of true progressive muscular dystrophy. The pathological changes in muscle observed in polymyositis are very different from those of muscular dystrophy. Hence muscle biopsy is the only certain means of differentiation between the two conditions; this procedure should be carried out in any atypical or unusual case of proximal muscle weakness, since the prognosis of polymyositis is very much better than that of dystrophy and improvement after treatment with ACTH or perhaps wheat-germ preparations is possible.

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AN UNUSUAL TYPE OF PRE-SENILE DEMENTIA

(Atypical Alzheimer's Disease with Amyloid Vascular Change)

BY

J. A. N. CORSELLIS and J. B. BRIERLEY

(From the Neuropathological Laboratory, Runwell Hospital, Wickford, Essex, and the Department of Neuropathology, the Institute of Psychiatry, Maudsley Hospital, London)

In 1927 Divry established that the central core of many senile plaques behaved like amyloid. Later (1934) he showed that this was also true of Alzheimer's neurofibrillary tangles.

In 1938 Scholz described an amyloid change of the blood vessels which he had found not uncommonly to occur in the ageing brain. On account of its possible relation to the origin of senile plaques the change was called by him "drusige Entartung" (plaque-like degeneration). Its clinical implications were not discussed; it had twice been found to occur below the age of 70.

In 1940 Worster-Drought, Greenfield and McMenemey described the clinical and pathological findings in an unusual form of pre-senile dementia with spastic paralysis. In the same year van Bogaert, Maere and de Smedt, when discussing the "early familial forms of Alzheimer's disease," reported the findings in an "heredo-familial case of dementia with spastic paraplegia." In 1947 Lüers described two siblings both of whom died demented, at a pre-senile age and with signs of a spastic paresis of the lower limbs.

In all these cases, and in a second one from the original family (Worster-Drought, Greenfield and McMenemey, 1944) there was an unusual histological picture which, while showing to a variable extent the feature of Alzheimer's disease, also showed a most severe form of amyloid vascular change. This was identified both by van Bogaert, Maere and de Smedt (1940) and by Lüers (1947) as the plaque-like degeneration of Scholz. In the cases described by Worster-Drought, Greenfield and McMenemey (1940) and by Lüers, attention was also drawn to a remarkable type of plaque formation.

Apart, therefore, from the intrinsic interest of an amyloid change taking place in the brain, whether genetically determined or not, these

cases are of additional importance since at first sight they appear to form a fairly clear-cut clinico-pathological entity.

For these reasons it is perhaps justifiable to describe two further cases unrelated to each other. In the first of these hereditary factors may well have been important, while in other ways both resemble the earlier ones.

Case 1.—E. W., a female aged 53, was admitted to Warley Hospital, Essex, in April 1952 and died in August of the same year. As by the time of her admission she was too demented to give any clear account of herself the following description is that given by her relatives.

For many years the patient had sat at home while her husband and children did the housework and shopping. About five years before her admission she began to complain of severe headaches which lasted for weeks on end and finished with dizzy spells and falling about. Six months before admission she had a "stroke" (affecting her right leg) and the headache became less frequent. From that time on, however, anything she attempted was wrongly performed—coal in the oven instead of the fire, dishes wiped with the first thing to hand. Her memory became faulty. There were periods of staring at nothing for hours on end. She was unable to dress herself, twisting her clothes over and over. The weakness of the right leg became worse, the toes of the right foot grating on the ground. She was cold all the time.

On admission she was described as pleasant, fatuous and childish. She was restless in an aimless way. Her memory was bad and she found difficulty in answering questions. She gave her age as 7 and said that she had left school at 12. She had no idea of the date or even of the year; she could not say where she was. She had to be hand-fed and was doubly incontinent.

On examination there was some degree of a mask-like facies with infrequent blinking. The pupils were unequal and irregular, the left smaller than the right. The reaction both to light and accommodation was normal. Sensation was apparently normal and no impairment of co-ordination was found but co-operation was extremely poor. The upper limbs and the left leg showed a slight increase in tone, but their power was good and the reflexes equal and normal. There was definite weakness of all movements of the right leg and the limb was spastic. The knee-jerk and the ankle-jerk on this side were exaggerated. There was no ankle clonus. On the left side the plantar response was flexor, on the right equivocal. When the patient walked she dragged her right foot, which was bruised and scratched.

Her blood pressure was 170/95. The Wassermann reaction in the blood was negative. The cerebrospinal fluid was under normal pressure and the cell count and protein level were normal. The W.R. was negative. The Lange curve 1111000000.

During the following three months the patient became very much more restless and confused and was unable to understand the simplest commands. She died, mute and completely demented, four months after admission, at the age of 54. The illness had lasted at least three years.

Family history.—Particular attention was drawn to the family history by the patient's husband and by her son. The latter was concerned about marriage since a similar illness had affected both his grandmother and one of the patient's brothers.

It was then established that the patient's mother died aged 55. For some years before death she had been extremely inactive, but in the last three years of her life she had deteriorated mentally while clinically she had been diagnosed as a case of disseminated sclerosis. From the descriptions given by her relatives it is clear that she became demented at a pre-senile age but the clinical records have unfortunately been destroyed.

An elder brother of the patient died aged 40 in a mental hospital. He had deteriorated both mentally and physically for some years before this. Two years before his admission it had been noted that his memory was faulty; he had no conversation and no inclination to do anything. He was depressed at times but did not complain of headaches. It was noticed that he walked badly. On admission to hospital he was unco-operative, listless, wet and dirty. He continually made restless, aimless movements; he looked vacantly around, not appearing to know where he was. He could obey a very simple command. Occasionally he uttered a meaningless jumble of words. On physical examination he was found to be in poor health with evidence of bronchiectasis. His pupils were irregular. His speech was slurred and he had a trombone tongue. There was wasting of all his limbs with marked loss of power. The tone was noted as poor. In the upper limbs his biceps-jerks were increased. In the lower limbs the knee-jerks but not the ankle-jerks were increased. The plantar responses were equivocal. No further information was available and he died a few weeks after admission.

One brother is alive and well, aged 63, and so is one sister aged 46. One sister died aged 55, but the cause is unknown. Two siblings died in infancy.

The patient had 3 children—2 are alive and well, a boy aged 22 and a girl aged 16. The firstborn died in infancy—"something wrong with the back, a dent in the spine."

Post-mortem examination.—This was performed 24 hours after death. The body was wasted and the skin broken over the buttocks. The cause of death was found to be bronchopneumonia, but beyond the fact that all organs other that the lungs appeared normal to the naked eye, no further observations were made. The uncut brain was fixed in 10 per cent formalin.

Macroscopic appearance of the fixed brain.—The weight of the fixed brain was 1,265 grammes. The leptomeninges over the vertex and the convexity were milky and slightly thickened but there was no shrinkage of the convolutions. The blood vessels appeared normal and there was no evidence of arteriosclerosis. On the right side, however, the meninges over the supramarginal, the angular and the middle two-thirds of the posterior central gyri were stained brown and the cortex below was bulging and felt soft. Underlying this, at the junction of cortex and white matter, was a small cystic area (about 1 cm. across) with brown coloured walls. A similar cavity, but without the staining, was present in the centre of the splenium of the corpus callosum and both the splenium and the adjacent bodies of the fornices felt soft. The white matter of the hemispheres, and of the occipital lobes in particular, contained many minute holes and in places seemed unduly friable. Occasionally a small hæmorrhage (2-3 mm. diam.) had occurred within the cortex. The ventricles were not dilated and no other abnormality was noted.

Histology of the brain.—Plaque formation: With low magnification and with any routine staining method the most striking finding was the appearance of vast numbers of small, round, almost structureless, bodies (50–100 μ in diameter) scattered throughout all the layers of the cortex and present in all the cortical areas examined. No attempt at counting was made but they were probably most numerous in the subiculum and the hippocampal formation. The cingular gyrus and insula were also severely affected; the frontal, central and parieto-occipital gyri slightly less so. At subcortical levels large numbers were found in the striatum, especially the putamen and in the claustrum (fig. 1); many in the amygdaloid nucleus; fewer in the thalamus, and a few were scattered in the tectum of the mid-brain. The pallidum, pons, cerebellum and medulla were unaffected.

The most unusual feature about this was the fact that these bodies, while being reminiscent of "senile" plaques could yet be identified so readily and in such large numbers without the use of special methods. Myelin staining, for example, brought

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them out by contrast in the deeper layers of the cortex and subjacent white matter where they appeared as clear-cut oval discs, either breaking the continuity of the myelin sheaths or pushing them to one side (fig. 2). Cresyl violet showed them well, although usually unstained, in all layers of the cortex and especially in Ammon's horn (fig. 3). The centre occasionally stained a diffuse purple. The nerve cells around these bodies frequently appeared to have been displaced by them.

These plaques could also be identified by using iron hæmatoxylin and van Gieson's counterstain. This method revealed clearly a number of similar structures containing a yellow-brown core. In addition fragments of such "core" material were lying free in the tissue with no or only a faint surrounding halo.

In silver-impregnated sections all varieties of senile plaque were present (fig. 4), many appearing as no more than dark granular patches in the cortex. It was this latter, finely granular type, that appeared to correspond to the homogeneous discs seen with ordinary staining methods.

Sometimes the centre of a plaque consisted mainly of fragmented fibres. Occasionally a granular change had occurred round a small thickened vessel giving the appearance of a perivascular plaque. In addition many small lumps of deeply argentophilic material were also lying free, apparently unrelated to any plaque formation but at times seeming to have come from a vessel wall (fig. 5).

In sections stained with hæmatoxylin and Congo red the picture was very similar but now the central cores of the plaques and the free-lying substance stained red or bright pink. The granular appearance seen in so many of the plaques in the silver picture was not evident but the disc-like homogeneous type of plaque could again be identified in large numbers by what appeared to be a change in the density and pattern of the tissue rather than by any colour reaction (fig. 6). There is no doubt that such a plaque, homogeneous when stained with Congo red, would have a finely granular structure when impregnated with silver.

With Mallory's phosphotungstic acid hæmatoxylin the core of the plaques and the free-lying material appeared pink, with methyl violet and with one per cent toluidine blue they were reddish purple, with iodine they stained dark brown, and with Sudan III a very faint pink at times. When first stained with Congo red and then using Nicol's prisms they were doubly refractile, each fragment appearing as a Maltese cross. Mayer's mucicarmine stained them pink but much less intensely than the mucin in control sections of gut. Weigert's fibrin stain was negative. The periodic acid Schiff reaction (PAS) was positive but this is described in more detail under Case 2.

Large fibrous astrocytes had often encircled the various types of plaque (fig. 7) but only their processes appeared to enter them (fig. 8) while the microglial cells—which were considerably proliferated—gave the impression of lying usually within the plaques (fig. 9).

Alzheimer's neurofibrillary change.—This was present in a moderate number of nerve cells thoughout the cortex but in the subiculum it was exceptionally severe (fig. 10). The change was best seen demonstrated by Bielschowsky's or von Braunmuhl's silver methods but it could also be detected in Congo red preparations. In this instance faint anisotropism was present.

Blood vessels.—A further group of striking changes were those affecting the small meningeal and the cortical vessels. While such changes were present in all areas of the leptomeninges and the underlying cortex they were more marked in the posterior half of the brain and most intense in the right occipital lobe and especially the striate area. They were not seen in the brain-stem and only to a mild degree in the striatum. The changes were of two main types: firstly, the walls of the cortical arterioles were grossly thickened and almost homogeneous in appearance. They stained pink with eosin or with cresyl violet (fig. 11). In orceïn and van Gieson stained sections the change was seen to lie outside an attenuated and poorly staining

elastic lamina and to affect the middle coat which stained a brown-yellow (fig. 12). Often no elastic lamina could be identified. Toluidine blue stained such a thickened vessel reddish purple and mucicarmine stained it pink. Fibrin staining was negative.

With Congo red such a vessel stained red and was then doubly refractile (fig. 13). The intima was usually intact but the fibres of the inner layer of the media appeared swollen, their structure blurred and no nuclei could be identified. Surrounding this was a complete band of amorphous material which with high magnification, however, gave the suggestion of a reticulated or radial structure (fig. 14). At times this substance appeared to erupt like a small wart growing on the outer side of the vessel wall while fragments of a similar substance were seen lying free in the cortex. Sometimes the background was completely unaltered around these fragments (fig. 6) but often there was the suggestion of a plaque-like halo. Since in the latter case the appearances and staining reactions then approximated to those of typical laminated plaques it is conceivable that, as Scholz maintained, this was the origin of all such plaques. It seemed more probable, however, that the majority, both core and haloes, were formed independently of the vascular detritus.

No connexion between the vascular changes and the homogeneous type of plaque was demonstrated.

Secondly, while the middle coat of the smaller meningeal vessels was similarly affected (the larger meningeal vessels were intact) in both these and in the cortical arterioles an intimal thickening had also occurred at times. In this instance, however, it was a typical fatty and hyaline change, staining red with Sudan III and often containing a few foam cells in the deeper layers. It was not stained by Congo red nor was it doubly refractile. Occasionally both the intimal and the middle coat changes were present together and the whole vessel wall might then become converted into a homogeneous mass (fig. 15). When stained with orceïn and Congo red the thickened intima stained a light purple, the remnants of the elastic lamina black and the middle coat, when still identifiable, red, so that the mixed nature of the vascular disintegration could be demonstrated, for a vessel only showing the altered media did not appear to break up in this way. Such a degenerating vessel was often encircled by an area of hæmorrhage; at other times by a cuff of iron-containing pigment, microglial cells and fibrous astrocytes.

The capillaries and some of the cortical arterioles did not show these changes but were then often surrounded by large perivascular spaces which were interlaced by a very fine network of fibres. Many of the smaller meningeal vessels showed in addition to the changes in the media some degree of intimal proliferation and fibrosis.

In sections stained with cresyl violet the cerebral cortex appeared severely damaged. In addition to the distortion of the cell pattern by the plaque formation there were many areas of localised loss of nerve cells and a secondary gliosis. In the orbital frontal cortex for example, this was so marked that the various layers could no longer be identified (fig. 16). In the central, parietal and occipital areas such focal changes were less pronounced but there was nevertheless a diffuse loss of nerve cells.

An extremely dense glial fibrosis was present in the outer layers of the cortex and a moderate astrocytic proliferation, especially in relation to the plaques, had occurred in all layers. Occasionally there was a glial scar round a hyalinized vessel.

Throughout the white matter of the hemispheres there was a patchy loss of myelin. This was most marked in the right parietal and occipital lobes (fig. 17) and in the splenium of the corpus callosum. In other regions the myelin was thinned and many small softenings had occurred. Within the white matter the walls of the blood vessels were not thickened in any way but, as with a number of the cortical vessels, the perivascular spaces were frequently dilated and were then spanned by a fine fibrous network in which many microglial cells containing iron pigment and

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some foam cells were often seen. The white matter contained many metachromatic bodies.

A moderately severe glial fibrosis was present throughout the white matter but it was usually at its most intense where there had been some degree of demyelination.

In the cerebellum there was a patchy loss of Purkinje cells in many folia but this was nowhere marked. Neither with the usual staining methods nor by the Gros-Bielschowsky method could any plaque formation or amorphous substance be identified. A number of the smaller meningeal vessels showed a change of the media similar to that already described but this was limited in extent. There was no appreciable demyelination.

No plaque formation or vascular change was seen in the pons or medulla and these were normal in other respects. The choroid plexus contained a number of corpora amylacea but the vessels showed none of the changes already described.

Case 2.—A. S., a female aged 65, was admitted to Friern Hospital, New Southgate, in May 1950, and died there thirteen months later. The information about the period before admission had been obtained from her relatives.

The patient was the second eldest of a family of 8 and was regarded as its most intelligent member. She ran a guest house and was hard working until the onset of her illness in 1941. She then developed "a vacant air about her" and appeared to have difficulty in recognising people. She was able to continue running the guest house for a further six years. When on holiday at this time she began to wander about at night. Subsequently her memory began to fail and she became increasingly confused and resistive. She muttered continuously to herself and became unable to answer questions. Her habits were faulty.

On examination at the time of admission (nine years after the onset) she was found to have small, regular pupils, which reacted normally to light and accommodation. There was no disturbance of muscle power or tone and the tendon reflexes were normal, the plantar responses being flexor. The blood pressure was 140/100 and the cardio-vascular system was described as normal.

In July 1950 a physician reported that "it would appear that both her sensory and motor speech areas are grossly involved in either a generalized cerebral arteriopathy or Alzheimer's disease."

Epileptiform seizures began in September 1950 and occurred about once a month up to the time of death.

By January 1951 she was doubly incontinent, grossly demented and quite inaccessible. In March 1951 it was reported that "she has a severe degree of spastic rigidity of all limbs." She died in June 1951.

Family History.—The patient's mother died aged 67, having had to give up her work as a charwoman "because of failing powers." She was nursed at home until two years before her death when she was transferred to an infirmary, death being due to "senile decay."

Of the 7 other siblings 2 were killed in the last two world wars and one sister died in childhood (cause unknown). The first and third are described as normal. The fourth is considered very temperamental and unstable. The second brother had a nervous breakdown twenty years ago and has since worked as a warehouse porter. He appears dull, anxious and dependent.

In conjunction with a psychiatric social worker, several further attempts have been made to amplify the family history, but the surviving siblings have unfortunately failed to co-operate and nothing useful can be added.

Post-mortem examination.—The cause of death was found to be bronchopneumonia and apart from the lungs no naked-eye abnormalities were described. The brain was fixed uncut in 10 per cent. formalin.

Macroscopic appearance of the fixed brain.—The weight of the fixed brain was 1,280 grammes. There was considerable atheroma of the basal vessels. The

leptomeninges were moderately opaque. No other abnormality was seen on the surface. On coronal section the third and lateral ventricles were slightly dilated and the ependyma appeared frosted. The blood vessels of the white matter in all regions were surrounded by lacunæ and often appeared tortuous and shrunken.

There was a single small cavity (1 cm. diam.) in the white matter of the posterior part of the right temporal lobe. Its walls were smooth and rubbery. No other evidence of softening was found.

Histological appearances.—The leptomeninges showed slight fibrous thickening. There was some astrocytic proliferation and glial fibrosis in the superficial layers of the cortex, especially in the occipital lobes. The laminar pattern of the cortex was not greatly disturbed.

In myelin-stained sections of the frontal lobe (Heidenhain's method) while the arcuate fibres appeared intact, the central white matter showed slight rarefaction. The perivascular spaces were greatly dilated in all regions but most severely in the occipital lobes. There was a mild patchy (largely perivascular) glial fibrosis throughout the white matter of the hemispheres, again greatest in the occipital lobes. The internal capsule, cerebral peduncles and fibre tracts of the brain-stem showed a mild gliosis but this was not greater than that seen elsewhere.

The most prominent histological findings, however, were the plaque formation and the vascular changes.

Plaque formation: The plaques in general resembled those seen in the first case but were less numerous and conspicuous. Again, they were visualized by all routine methods. Thus in myelin-stained sections they appeared as punched-out discs, empty except for an occasional fibre sheath. Cresyl violet showed many plaques to have a central blue core and a pale mauve halo. With iron hæmatoxylin and van Gieson's stain they were seen as yellow orange discs sometimes containing a darker orange core.

The plaques were entirely absent from the caudate and lentiform nuclei, thalamus, claustrum, subthalamic nucleus, substantia nigra, cerebellum and brain-stem.

In silver impregnations the great variability of the plaques both in form and size was well displayed. They ranged from small homogeneous discs to large laminated structures consisting of a dark compact core surrounded by a clear halo and this in turn by a granular ring. Some perivascular plaques were also seen, usually eccentric and consisting of a dark core immediately adjacent to the vessel wall and surrounded by a granular periphery, the whole structure occupying a part of a dilated perivascular space (figs. 18 and 20).

Groups of fibrous astrocytes commonly occurred in close relation to, but always outside the plaques so that in Holzer preparations the plaques could be identified by the presence of collections of astrocytes round part or the whole of their circumference. Many microglial cells were seen to lie outside the plaques each sending a process into the interior. Less frequently, several distended microglial cell bodies lay within the plaque, a single process emerging through the surface. Occasionally a group of swollen and distorted microglial cells occupied the centre of a plaque.

Appearances closely similar to the first case were obtained in sections stained with hæmatoxylin and Congo red, the plaque cores and free-lying masses staining red and the homogeneous plaques being suggested as discs of a finely granular structure. Subsequent examination under polarized light showed both the plaque cores and the free-lying masses to be doubly refractile.

Alzheimer's neurofibrillary change: This change, although nowhere very conspicuous, was present in many of the nerve cells of the deeper cortical layers. It was most marked in the occipital and virtually absent in the frontal cortex. It was not seen in the corpus striatum, thalamus or brain-stem. The altered neurofibrils were also recognizable in Congo red preparations (they were then also doubly

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refractile) and they were clearly visible as brown threads in sections stained by King's method for amyloid.

Blood vessels: Striking abnormalities of structure were observed in the small vessels of the meninges, cortex and white matter and were most marked in the occipital lobes, absent in the brain-stem and cerebellum and only occasionally seen in the striatum and thalamus. Two types of change were present. One involved the cortical arterioles only and consisted of a gross thickening of the tunica media which was converted into a homogeneous layer staining pink with cresyl violet, brownish yellow with van Gieson's stain (fig. 19) and red (and doubly refractile) with Congo red. The staining reactions of this modified middle coat differed in no important respect from those of the plaque cores and the free-lying amorphous masses in the cerebral cortex.

The second type of vascular abnormality occurred in small meningeal vessels and in some cortical arterioles and consisted of an intimal thickening of fatty, hyaline nature giving positive staining for fat and containing a few foam cells. This intimal layer did not stain with Congo red and was not doubly refractile. The elastic lamina was either fragmented or absent and the media thickened and almost structureless. In many instances when the elastica was absent it was not possible to identify separate intimal and middle coats.

Vessels undergoing this type of change often lay within dilated perivascular spaces or were surrounded by globular hæmorrhages. The vessels of the white matter presented a similar picture except that the perivascular spaces were larger and filled with fine trabeculæ.

In the choroid plexus gross fibrosis was constantly seen in the larger arteries while many capillaries appeared normal; others showed various degrees of fibrosis up to total occlusion. Fatty, hyaline thickening of the intima and fibrosis were seen in many arteries which resembled that seen in the meningeal vessels. Occasionally such changes were associated with thrombosis.

The following investigations were carried out on material from both cases.

Periodic Acid Schiff reaction (*PAS*), as described by Wislocki and Singer (1950). At first frozen sections from blocks washed overnight in running water were used although later it was found that sections from which the celloidin or paraffin had been removed gave comparable results.

In both cases the salient microscopic features were the bright bluish-red staining of many plaque cores which appeared either as discs with well-defined or fluffy edges or as clustered irregular masses within an unstained halo. Occasional perivascular patches of dark pink staining were seen in the cortex closely resembling those seen in the Congo red and toluidine blue preparations.

In blood vessels of all calibres the intima and adventitia were stained red and the intervening hyaline material, when present, was a faint to dark pink colour. Discrete red staining masses not identifiable as plaques were rare and seemed to occur in close relation to arterioles and capillaries.

When the PAS technique was carried out on sections previously impregnated in Rossman's fluid (Hess, 1953) for forty-eight hours the plaque cores stained bright pink and the vascular hyaline material various shades of pink. The capillary network was well displayed and it was of interest to note that plaques were frequently seen in contact with or close to capillaries that were irregularly contracted, occluded, surrounded by a dilated pericapillary space or occasionally forming the centre of a plaque itself.

It may be concluded from these results with the PAS technique that the plaque cores, the irregular perivascular patches, the free-lying masses and to a lesser extent the homogeneous vascular material are all PAS positive suggesting the presence of a common substance, probably a mucopolysaccharide or a mucoprotein (Hess, 1953).

McManus (1948) has pointed out, however, that substances other than

mucopolysaccharides may yield an aldehyde on hydrolysis. In view of this the presence of free α-aminoacids in the protein component of the amyloid-like material was tentatively excluded by the negative result with Feigl's reaction (1946) in which frozen sections from material impregnated in Rossman's fluid were treated with 2 per cent. sodium hypochlorite in place of 1 per cent. periodic acid of the PAS method.

The presence of free lipid was also eliminated by bringing sections from which the celloidin had been removed to either water or 90 per cent. alcohol. Each group was then treated with either hot (under a reflux condenser) or cold chloroform ethanol mixtures. All sections were then submitted to the PAS technique and on examination showed that apart from the white matter, which was now colourless, there was no alteration in the degree or distribution of staining.

The possibility remains, however, that lipid may still exist in the plaques and blood vessel walls, not in a free state but in combination with protein. Moreover such a proteo-lipid complex on contact with alcohol and formalin during embedding might be expected to undergo some change akin to denaturation which would render it even more resistant to extraction by solvents.

Metachromatic staining.—Formalin-fixed frozen, celloidin and decelloidined sections from both cases were stained with 1 per cent. toluidine blue for up to thirty minutes. Clear evidence of metachromasia was seen in the pink staining of the cores of many plaques, in the homogeneous thickening of the blood vessels and as occasional free-lying masses. Diffuse lavender-coloured patches were also observed in the tissue adjacent to the walls of many arterioles and capillaries, an appearance resembling that seen with Congo red and PAS methods. There were many reddish-pink "metachromatic" bodies in the white matter.

Treatment of the sections with either hot or cold chloroform ethanol mixtures abolished the metachromasia of the white matter but did not affect that of the plaque cores or blood vessels. The metachromasia was much reduced and at times abolished by dehydration through the alcohols, subsequent to staining (it was at its most intense in celloidin sections mounted in glycerine jelly).

Walton (1954) has recently demonstrated a relation between the degree of metachromasia obtained with toluidine blue and the acidic, and especially sulphate, groups of a parent polysaccharide. Since the metachromasia was marked in both cases the possibility that it was due to the sulphate content must be considered, but the fact that it was greatly reduced by subsequent treatment with water and alcohol may be evidence against this conclusion (Pearse, 1953).

The other acidic groups likely to be responsible are either a phosphate or hyaluronic acid. The former, according to Wislocki and Singer (1950) causes only slight metachromasia and the inference is that the latter may be of more importance, but its identification is beyond the scope of the present investigation.

The Identity of the Abnormal Substance

The abnormal substance found in both these cases in the plaque cores, blood vessel walls and as free-lying fragments was faintly visible in unstained sections. It was much more clearly seen in almost all routine staining methods including hæmatoxylin and eosin—when it appeared pink, and hæmatoxylin and van Gieson's stain—when it was brownish-yellow.

It stained dark brown with iodine and exhibited metachromasia with 1 per cent methyl violet and 1 per cent toluidine blue. It stained dark

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brown or black with King's silver method; Congo red stained it bright pink or red and it was then birefringent.

Since these are the reactions generally ascribed to amyloid it seems reasonable to use this term without qualification in the subsequent discussion. This should not, however, be taken to imply any closer relation to amyloid, as found elsewhere in the body, than that suggested by the evidence of the above staining reactions. It might be emphasized that the chemical nature of amyloid wherever it is found is not clearly defined.

In the first case the substance stained at times very faintly with Sudan III. In both cases Mayer's mucicarmine stained it pink but this was considerably less intense than that of the mucin in control sections of gut. Weigert's fibrin stain was negative.

In the present cases the indications are that the common substance is an acidic complex, probably a mucopolysaccharide.

Discussion

While there is no complete proof that the first patient reported here was suffering from an hereditary condition there is some evidence to support the suggestion. A brother of the patient had died in a mental hospital at the age of 40 of what appeared clinically to be a similar condition. Their mother died at the age of 55, having deteriorated in the same way mentally while a diagnosis of disseminated sclerosis had been made clinically.

In the second case the patient's mother died aged 67 of what was described as "senile decay." Two male siblings (aged 56 and 52 at interview) gave an impression of mental dullness. There is therefore only slight evidence in favour of a possible hereditary factor.

With regard to the diagnosis during life, in the first case it could only be inferred that the condition was due to "a widespread and diffuse degeneration of unknown kind . . . a pre-senile atrophy." In the second case the clinical diagnosis had been that of "either a generalized cerebral arteriopathy or Alzheimer's disease."

In both cases the brain was normal in size, no marked loss of weight was found and no shrinkage of the gyri could be seen with the naked eye. Nevertheless the obvious diagnosis—in view of the ages and of the widespread plaque formation and neurofibrillary change—was Alzheimer's disease. As described already, however, and especially with regard to the first case, the strikingly unusual appearance of so many of the plaques and the remarkable ease with which they could be recognized with any staining method made this diagnosis less certain. The position was further

obscured by the amyloid vascular changes which were present in both cases and by the demyelination, which was more marked in the first.

The vascular changes were undoubtedly the same as those described in detail by Scholz (1938) and called by him "drusige Entartung." Their appearance, their staining reactions and the presence of anisotropism all support this conclusion.

In both cases, but mainly in the first, a number of cortical and pial vessels also showed a fatty and hyaline change of the intima (identical with the "Hyalinose" of Scholz and Nieto, 1938).

The main differences between the two cases are that in the second there was severe atheroma of the larger vessels, less demyelination and a less intense plaque formation. Clinically this case was twelve years older than the first patient and showed no unusual neurological features until shortly before death. It therefore differs from the first case and the two are not entirely comparable. Both cases, however, appear to demonstrate a morphological link between Alzheimer's disease, the amyloid form of senile vascular disease and the group of hereditary cases mentioned in the introduction.

This group is made up of the families reported by Worster-Drought, Greenfield and McMenemey (1940, 1944—Cases 1A and 1B of table overleaf, pp. 582–583): van Bogaert, Maere and de Smedt (1940—Cases 2A, B, and C of table); and Lüers (1947—Cases 3A and 3B of table). The clinical findings in each of these cases and in the present ones (Cases 4A and 5 of table) are summarized below:

In each case there was a progressive dementia coupled with the development of a spastic paresis or paralysis, although the latter finding was not so predominant a feaure in Case 5 of the table as in the others. In the earlier cases there were signs of cerebellar disease which were not present in either of the 2 cases now reported.

The pathological findings are also summarized in the table. It is noticeable that the weights of the brains are on the high side for an atrophic condition while macroscopic shrinkage of the convolutions was only slight or absent.

From the histological point of view plaque formation was present in all 7 cases and in 6 considerable emphasis has been laid on the unusual appearance of many, or all of them. In Cases 3A and 3B only the homogeneous kind was present and Lüers described them as "remarkable condensations of the cortical ground substance." In Cases 1A and 1B both the homogeneous and the cored variety of "plaque-like structure" were present (as well as typical senile plaques). In Case 4A (and to a lesser

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REPUTED CASES OF PRESENILE DEMENTIA WITH SPASTIC PARALYSIS

Family	1 Worster-Drought, Greenfield and McMenemey (1940, 1944)	2 van Bogaert, Maere and de Smedt (1940)	3 Lüers (1947)	4 Present case	5 Present case
Case number	1A	2A	3A	4A	5
Sex	Male	Male	Male	Female	Female
Age: onset	47	25	26	51	56
death	54	39	41	54	66
Summary of clinical history	Onset of difficulty in speaking, lack of interest, and defective memory. Cold. Gait became slow, ataxic, finally spastic paralysis	Onset of a slowly progressive paraplegia. Falling over, dragged left leg. Severe mental changes with gross memory and speech defects. Finally complete dementia	Onset of headaches, slow speech and slow gait but "mental changes were for a long time less prominent than the neurological." Cold legs. Falling over, later couldn't stand or walk. Complete dementia with spastic paraplegia	Onset of headaches, lack of interest and bad memory. Cold all the time. Progressed to complete dementia. Falling over, later dragged her right leg, spastic paresis	Onset of carelessness, vacant look, faulty memory. Finally completely demented. Nervous system normal two months before death, then generalized spasticity of all limbs
Cranial nerves Summary of neurological findings.	Slight tremor of tongue. Pupils normal at first, later unequal	Face inexpressive, rigid. Right facial weakness	Unmoving, stiff facial appearance. Tremor of tongue	Some degree of mask-like facies. Pupils unequal and irregular	
Upper limbs	Power normal, tone increased, reflexes exaggerated	Tone increased, right arm held stiffly	Tremor of hands with lack of co-ordination. Some loss of power, increased tone	Reflexes normal, no increase in tone	No abnormality found in c.n.s. until two months before death. Then generalized spasticity of all limbs
Lower limbs	Increase in tone R>L. Jerks exaggerated. Finally bilateral ankle clonus and legs very spastic	Tremor of right leg, spastic paraplegia with jerks much increased. P.R.s both extensor	Spastic paralysis with increased reflexes and "pyramidal" signs	Paresis of right leg, spastic, jerks increased	
Abdominal reflexes	Absent	Absent	Absent		
Cerebrospinal fluid	Protein: 110 mg./100 ml.	Normal		Normal	
Blood pressure	155/90		140/80	170/95	140/98
Summary of pathological					

Summary of pathological findings.

Brain weight	1,340 grammes	1,230 grammes	1,440 grammes	1,265 grammes	1,280 grammes
Appearance	Slight frontal atrophy, vessels normal	Slight frontal atrophy, vessels normal	No atrophy, vessels at base normal; cortical vessels slightly prominent	No atrophy, vessels normal, Small cystic softening in parietal lobe	Some enlargement of ventricles. Marked atheroma of vessels at base
Plaque formation	*Ammon's horn, cerebellum:* clear round bodies 12-100μ. More structured ones had densely staining central mass. *Cortex:* occasional typical senile plaque	*Cortex, striatum, cerebellum:* all varieties of senile plaque	*Cortex, Ammon's horn, striatum, cerebellum:* masses of homogeneous plaques. No other type present	*Cortex, Ammon's horn, striatum:* masses of homogeneous plaques. Many typical senile plaques	*Cortex:* many homogeneous plaques and other typical senile plaques as well
Vascular changes	Pial, white matter and cortical arterioles showed hyaline swelling of media, no nuclei, yellow-brown with van Gieson, red with Congo red, unusually refractile	Scholz's "plaque-like degeneration" present in cortical vessels, rarely in pial	Scholz's "plaque-like degeneration" in many small cortical arteries and capillaries, "Hyalinosis" in some pial and cortical vessels	Scholz's "plaque-like degeneration" in many small cortical and pial vessels. Fatty, hyaline change in a few of such vessels	Scholz's "plaque-like degeneration" in many small cortical and pial vessels. Atheroma of larger vessels
Neurofibrillary changes	Present in Ammon's horn but not elsewhere in cortex	Present throughout cortex, especially Ammon's horn	Present in cortex and especially in Ammon's horn	Present in Ammon's horn and throughout cortex	Present in cortex, not in Ammon's horn
Myelin and glial changes	Myelin for most part rarefied with fairly dense gliosis. Marked demyelination in occipital lobe and corpus callosum	Marked thinning of intra-cortical fibres. Unequal gliosis of white matter. Pyramidal tract gliosis	Fairly heavy gliosis both of white matter and sub-pial	Moderately severe patchy demyelination with thick but uneven gliosis. Marked sub-pial gliosis	Slight patchy demyelination, most marked in occipital lobe. Patchy gliosis
Summary of family history	1B.—Female. Died aged 51. History similar to 1A-progressive dementia and severe spastic paraplegia. (Path. same as 1A.) Many other members of family also affected	2B and 2C.—Siblings of 2A. Similar age group. Spastic paraplegia with mental changes, dysarthria	3B.—Sister of 3A. Pains and stiffness in leg. Limited movement. Paresis of both legs. Progressive dementia	4B.—Mother of 4A. Died at 55 demented, had been diagnosed as disseminated sclerosis. 4C.—Brother of 4A. Died at 40 in mental hospital, dement walked badly but no clear evidence of paralysis	Mother died of "senile decay." Little evidence of hereditary factor found

extent Case 5) this was again true—all types being found—although, unlike the earlier cases, none was seen in the cerebellum.

There appears therefore to be a considerable variation in the distribution, intensity and type of plaque formation in the various cases. Much the same is also true of the neurofibrillary changes, which while present in all cases, were limited in 1A and 1B to the Ammon's horn but were scattered through the cortex in the other four (2A, 3A, 4A, 5).

In all 7 of the cases examined histologically, however, a further common finding is the unusual type of vascular change. McMenemey (1952) has recently discussed these changes in connexion with Cases 1A and 1B and there seems little doubt that they are the same as those found in the remainder.

From the diagnostic point of view, however, the conclusions reached were not the same in the various cases. Lüers wrote "we rather incline to the view that this is a particular early form of Alzheimer's disease in which circumscribed areas of the brain are especially severely damaged as a result of the vascular changes so that the degeneration of an affected system follows."

van Bogaert, Maere and de Smedt placed less emphasis on the significance of the vascular changes in their case but classified it as one of Alzheimer's disease showing a "primary" system degeneration.

On the other hand Worster-Drought, Greenfield and McMenemey (1940) considered that their cases were not so closely related to Alzheimer's disease and that the ætiology of the condition "lay in a disturbance of the smaller vessels of the nervous system." Subsequently (1944) they invoked "a metabolic dyscrasia of the nervous tissue" as the probable cause of the vascular changes.

It seems likely, however, that similar vascular changes may also be found at times in otherwise typical cases of Alzheimer's disease (Benedek and McGovern, 1949; personal observations) and it is probable that all the cases under discussion are in some way related to this condition. At the same time they do appear to have a fairly distinctive pattern of their own and at least for the time being might be considered as a particular variant of Alzheimer's disease.

Such a suggestion is compatible with the presence of a "metabolic dyscrasia of the nervous tissue" since Divry (epitomized in 1947) has shown that such a process—that of "amyloid" formation—may well underlie the changes seen in Alzheimer's disease.

The possibility that amyloid deposits may have occurred in non-neural tissue of the present cases cannot be definitely excluded as no such tissues were available for histological examination. It can only be recorded that the naked-eye appearances of the viscera were normal. The limited amount

of histological evidence from the other recorded cases (Lüers) also suggests that such changes may be confined to the nervous system.

That the amyloid material under discussion is different in origin, if not in chemical nature, from that occurring in primary and secondary amyloidosis is suggested, however, by the rarity of the involvement of the nervous system in either of these conditions. Even when this does occur, it is the peripheral nerves and ganglia that are usually involved (de Navasquez and Treble, 1938; Denny-Brown, 1951; Fisher and Preuss, 1951; Andrade, 1952; Strich and Wade, 1953).

The even rarer involvement of the brain as well as certain thoracic and abdominal viscera has, however, been reported by Marinesco (1932) and Krücke (1950).

In addition to these isolated instances, the occurrence of amyloid in the brain has long been regarded by Divry as part of an ageing process and one which may occur at either a senile or pre-senile age (so correlating with senile dementia and Alzheimer's disease). In either group it may affect the cerebral vessels.

Very little appears to be known about the more precise composition of this form of amyloid, however, and it would in fact seem unwise to attempt to carry the discussion any farther. The immediate need is for more detailed information, on the one hand, of the physical and chemical structure of the amyloid substance and, on the other, of the occurrence—in similar cases—of this substance elsewhere in the body.

The most that is attempted here therefore is to draw attention to the existence of this unusual type of pre-senile dementia which combines features both of Alzheimer's disease and of vascular disease, the feature common to both appearing to be a form of amyloid change.

Summary

Two cases of pre-senile dementia are described. In the first case there was probably an hereditary factor present while in addition to the dementia there were also signs of a spastic paresis of one limb. Pathologically the findings were in part reminiscent of Alzheimer's disease but they also included a severe amyloid vascular change and plaque formation of unusual type and severity.

A remarkably similar clinico-pathological syndrome appears to have been described previously in three other families.

The second case of pre-senile dementia also showed the amyloid vascular change in addition to the more usual features of Alzheimer's disease.

The histological findings coincide with Divry's and with Scholz's observations on the amyloid basis of the various changes found at times both in the senile and pre-senile brain.

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The relation of these cases to each other, and to Alzheimer's disease and vascular disease is discussed, with a brief reference to amyloidosis in general.

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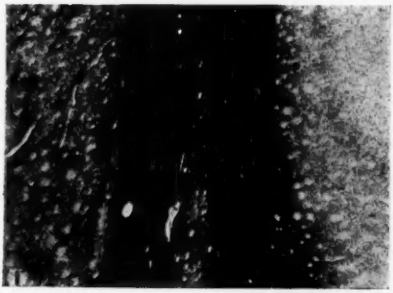
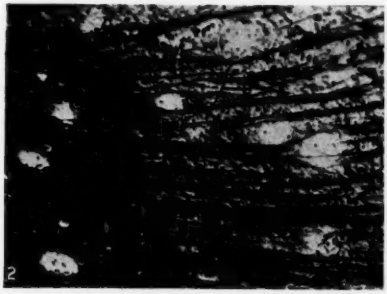
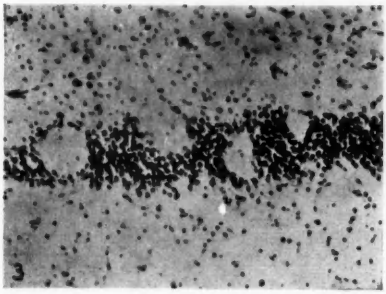
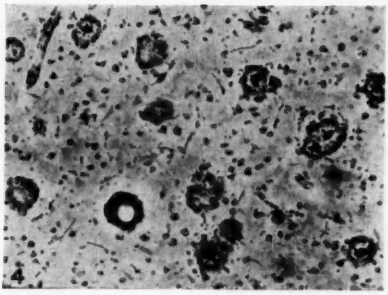
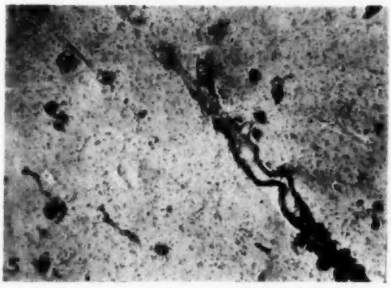
PLATE XII

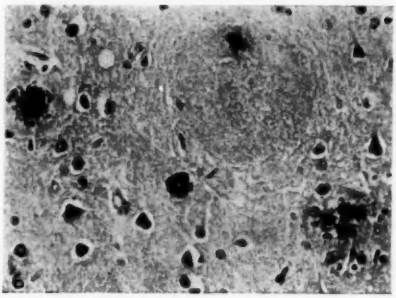


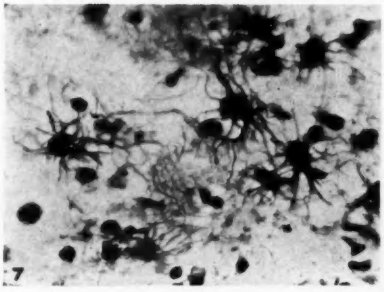


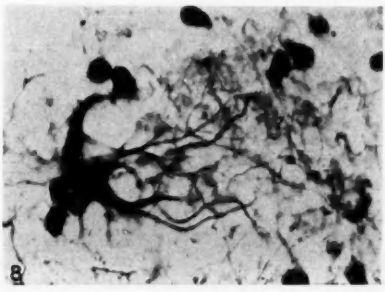






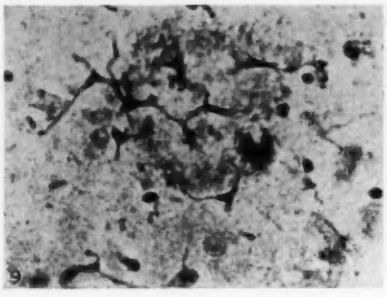


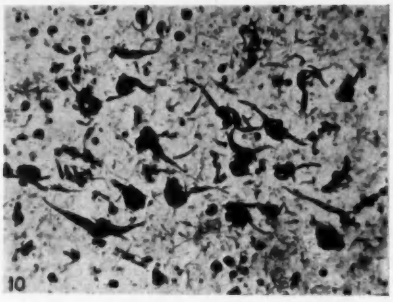


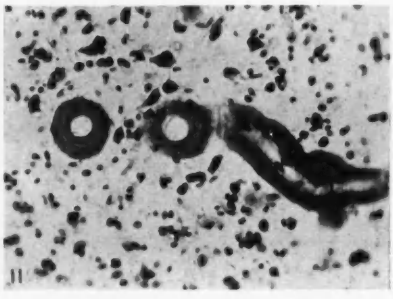


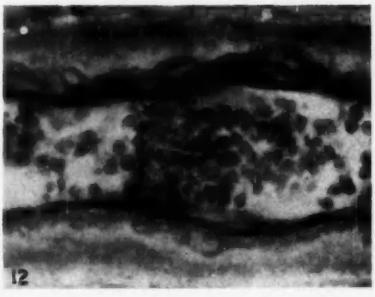
To illustrate article by J. A. N. Corsellis and J. B. Brierley.

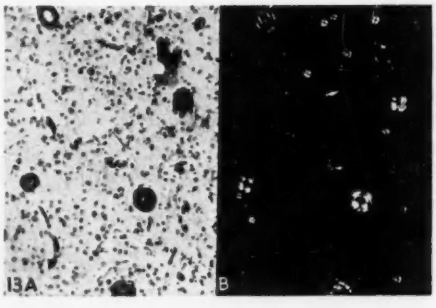
PLATE XIII

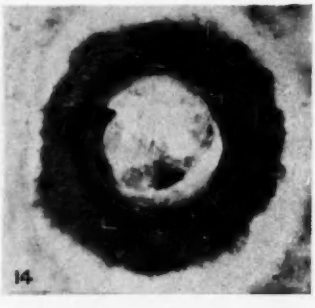






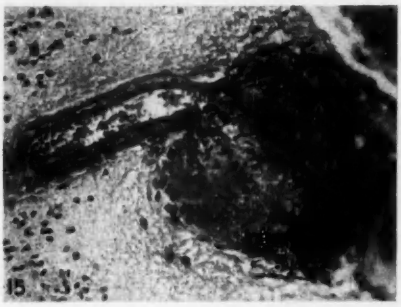


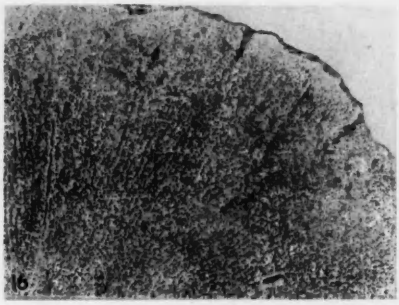


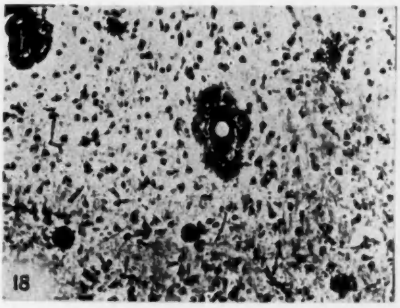


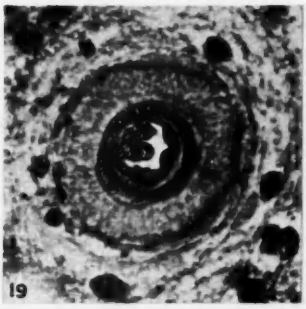
To illustrate article by J. A. N. Corsellis and J. B. Brierley.

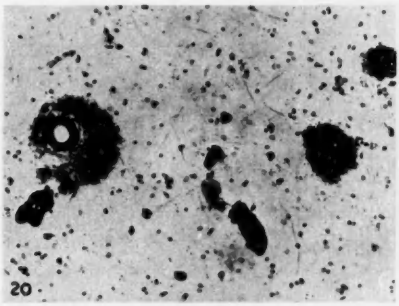
PLATE XIV











To illustrate article by J. A. N. Corsellis and J. B. Brierley.

XUM

LEGENDS TO PLATES

PLATE XII

FIG. 1.—Lateral border of putamen, the claustrum and cortex of the insula showing innumerable unstained plaques. Heidenhain method for myelin. × 12.

FIG. 2.—Junction of cortex and white matter showing the homogeneous plaque formations. Heidenhain method for myelin. × 90.

FIG. 3.—Homogeneous plaques in the dentate fascia. Cresyl violet. × 90.

FIG. 4.—All types of senile plaque, a few argentophilic patches and a thickened vessel. Hortega's silver method for astrocytes. × 90.

FIG. 5.—Plaque formations, mostly with a central core. Small fragments of argentophilic material similar to that forming the cores lying close to the vessel wall and other fragments free in the tissue. King's method for amyloid. × 84.

FIG. 6.—Fragments of amyloid substance lying in cortex and one homogeneous plaque (containing a glial nucleus at 12 o'clock) above and to the right of the central fragment. Congo Red and hæmatoxylin. × 180.

FIG. 7.—Fibrous astrocytes grouped round a homogeneous plaque. Holzer stain. × 180.

FIG. 8.—A large fibrous astrocyte, its processes penetrating such a plaque. Holzer stain. × 690.

PLATE XIII

FIG. 9.—Microglial proliferation in and around a plaque. Penfield method. × 345.

FIG. 10.—Alzheimer's neurofibrillary change in nerve cells of the subiculum. Bielschowsky method. × 90.

FIG. 11.—Cortical arteriole showing the marked thickening and the almost homogeneous appearance of the entire wall. Cresyl violet. × 180.

FIG. 12.—Longitudinal section of a vessel showing the considerable thickening situated mainly outside the elastica. (The white dots mark the outer limits of the vessel wall.) Orceïn, iron hæmatoxylin and van Gieson. × 690.

FIG. 13.—(*a*). Occipital cortex stained with Congo Red and hæmatoxylin. (*b*). The same field as (*a*), but under polarised light. The intense birefringency of the vessel walls can be seen as well as a number of small Maltese crosses which correspond exactly to the free-lying fragments of amyloid visible less distinctly in (*a*). (A) and (B) × 75.

FIG. 14.—Similar vessel to those in Figs. 11 and 12, but stained with Congo Red and showing the thickening and loss of definition of the middle coat and its reticulated halo (such a vessel is doubly refractile). × 550.

PLATE XIV

FIG. 15.—Cortical arteriole showing on the left the thickened middle coat. On the right there has been a fatty, hyaline change probably originating in the intima but the whole vessel wall is now swollen and degenerate. Orceïn and Congo Red. × 180.

FIG. 16.—Frontal (orbital) cortex showing the patchy loss of nerve cells and glial proliferation. Cresyl violet. × 15.

FIG. 17.—Moderately severe patches of demyelination on the right occipital lobe. Heidenhain's method for myelin.

FIG. 18.—Occipital cortex showing plaque formation round an arteriole with thickened walls. Hortega's silver method for astrocytes. × 90.

FIG. 19.—Cortical arteriole showing gross thickening of the middle coat with radial fibrillar structure (similar to that seen in case 1—Fig. 13). Iron hæmatoxylin and van Gieson. × 185.

FIG. 20.—Occipital cortex showing a large perivascular plaque, thickened blood vessels and two finely granular plaques. King's method for amyloid. × 90.

XUM

THE VALUE OF AXON RESPONSES IN DETERMINING THE SITE OF LESION IN TRACTION INJURIES OF THE BRACHIAL PLEXUS

BY

GEORGE BONNEY
Institute of Orthopædics, London

THIS investigation was undertaken to determine the value of certain reflex responses in locating the site of the lesion and in determining prognosis, in complete traction injuries of the brachial plexus. In the usual conception of such injuries (Seddon, 1948; Bonney, 1949) the site of the lesion is considered as being distal to the intervertebral foramina, but certain observations (Seddon, personal communication) have suggested that part of the lesion may be an avulsion of roots from the spinal cord. These observations—on patients showing the clinical picture of a complete and permanent degenerative lesion of the plexus—were firstly, the occasional finding of myelinated axons in the peripheral nerves of the affected limb, secondly, the occasional operative finding of an apparently undamaged plexus, and, thirdly, the occasional demonstration of ganglion cells in biopsy specimens of the plexus. These findings suggested the possibility of there being two types of traction lesion of the brachial plexus (fig. 1).

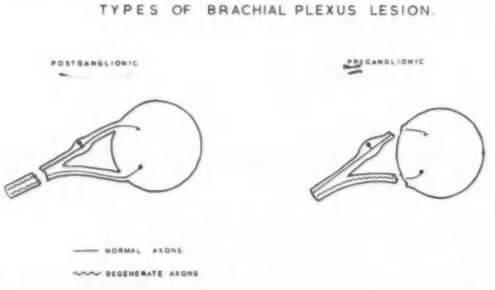


FIG. 1.—Diagrammatic illustration of conception of the two types of traction lesion of the brachial plexus. Showing mechanism of axonal degeneration in the post-ganglionic type, and preservation of peripheral axons of the posterior root system in the pre-ganglionic (intradural) type.

In the first type, the site of damage would be distal to the intervertebral foramen with consequent degeneration of peripheral axons, and with a

prognosis dependent upon the severity of the local damage. In the second type, the lesion would be an avulsion of roots from the cord, the peripheral axons of the posterior root remaining in continuity with their nutrient cells in the posterior root ganglion, and so remaining undegenerate. Such lesions clearly would have only a very remote chance of recovery. Although the clinical picture of motor and sensory paralysis would be similar in both types, axon reflexes (Lewis *et al.*, 1927) would be absent in the first type but present in the second. In the case of a mixed lesion, one area of skin might have no axon reflexes, while another, the nerves of which had suffered pre-ganglionic damage, would exhibit axon reflexes.

Axon reflexes were studied extensively by Lewis and his colleagues (Lewis *et al.*, 1927; Lewis and Landis, 1929; Lewis, 1930; Lewis, 1942), and by Greenfield and Shepherd (1950) but the first indication of their possible value in connexion with lesions of the brachial plexus was in 1948 (Bonney), when a normal triple response to histamine was demonstrated in the antebrachial skin of a patient who had suffered a complete and permanent lesion of the plexus. Later, Greenfield and his colleagues (1951) were able to demonstrate a normal finger-tip reaction to cold in a patient with a similar lesion. Exploration of the plexus in this patient had shown all the roots to be in continuity as far proximally as the intervertebral foramina.

Study of skin responses to histamine and of finger-tip reactions to cold forms with clinical and operative observations the basis of the present work.

Methods

(1) *Histamine response* (*as applied to cases of traction lesion of the brachial plexus*).—1/100 histamine acid phosphate was pricked into the skin of the forearm and of the dorsum of the hand. On the affected side six such punctures were usually made—two on the ulnar side of the forearm (probable root distribution T.1), two on the radial side of the forearm (probable root distribution C.6), one on the ulnar side of the dorsum of the hand (probable root distribution C.8), and one on the radial side of the dorsum of the hand (probable root distribution C.6 or C.7). As a control one or two pricks were usually made in the forearm or hand skin in similar dermatomes on the healthy side. The criterion of a normal reaction was the appearance of local vasodilatation followed by the formation of a wheal surrounded by a spreading flare. The reaction was classed as abnormal or degenerative if the response were by local vasodilatation and whealing only without the formation of a flare. The distinction between the two types of response was usually quite clear (fig. 2).

(2) *The cold vasodilatation response.* This was studied by thermo-electric measurement of heat elimination from the finger-tips, using the heat-flow discs described by Hatfield (1950). These consist of discs of tellurium, 7 mm. in diameter and 1 mm. in thickness, covered on both faces by fine copper gauze. When a disc is applied to a finger-tip immersed in cold water an electrical potential is developed between the two faces which is directly proportional to the heat-flow

from the finger-tip to the cold water. Each disc is calibrated in micro-volts per calorie per 100 cm.² per minute. Their use in this connexion was suggested by the work of Bonney, Hughes and Janus (1952) who had used them in experiments on heat elimination from the knee to water at 30° C. Usually two sets of observations were made on each patient, one after preliminary immersion of both hands for twenty minutes in water at 30° C., and one after preliminary immersion at 20° C. Only one experiment was carried out on each subject during one day. After drying of the hands a heat-flow disc was attached to the pulp of each finger under test by a thin Latex rubber fingerstall of such size as to exert no constriction on the digit. The fingers were then immersed to the level of the proximal interphalangeal joints in a bath of 10 litres capacity, containing water of a temperature of around 5° C., briskly stirred by an electric stirrer, the hands and forearms being comfortably supported at or a little below heart level. By occasionally adding blocks of ice to a cage in the water-bath the temperature could be kept constant to within 0·2° C. The bath temperature was kept uniform by the stirrer to within 0·1° C. Each experiment lasted between twenty and thirty-five minutes. The heat disc leads were connected through a junction box—enabling consecutive readings to be taken from up to 4 heat-flow discs—to a Cambridge spot galvanometer (resistance 27·4 ohms, 15 scale divisions per micro-amp.), a resistance box being interposed in series to allow galvanometer readings to be taken over the wide range of heat elimination produced. Since very accurate quantitative estimation of heat elimination was not sought, it seemed justifiable to assume a linear relationship between galvanometer deflection and heat elimination. From graphs constructed accordingly it was possible to convert galvanometer readings into an estimate of heat elimination in calories per 100 cm.² per minute. Wherever possible the reactions of the finger-tips of the affected side were compared with those of the finger tips of the healthy side. In the case of brachial plexus lesions, reactions of the second and fifth fingers of both hands were usually compared. The cold vasodilatation reaction was chosen for application to the finger-tips, as in this site the histamine response is difficult to assess. It was realized that such a vasodilatation could be elicited from a totally denervated finger-tip provided the previous warming had been sufficient (Greenfield *et al.*, 1951), and for this reason where a positive response was obtained after preliminary immersion at 30° C., a second test was usually done after preliminary immersion at 20° C. The occurrence of vasodilatation in the latter circumstance was taken as evidence of the presence of undegenerate peripheral axons.

The method used here of estimating cold vasodilatation has clear advantages over the thermo-couple method used by Lewis, as it enables much smaller variations in heat elimination to be detected. It is, however, less accurate than calorimetry as used by Greenfield and Shepherd (1950).

(3) *Muscle testing.*—In the patients with brachial plexus injuries, muscle power was graded in accordance with the system recommended in War Memorandum No. 7 of the Medical Research Council (1943), thus:

Paralysis	(0)
Flicker of contraction	(1)
Movement with gravity eliminated	(2)
Movement against gravity	(3)
Movement against gravity and resistance ...	(4)
Full power	(5)

Observations

Observations were made on 4 healthy subjects—2 male and 2 female—on 6 patients with peripheral nerve injuries, on 3 patients who had had

cervico-dorsal sympathectomies, and on 13 patients with complete traction lesions of the brachial plexus.

(1) *Healthy subjects.*—When (fig. 3) the finger-tip is immersed in water

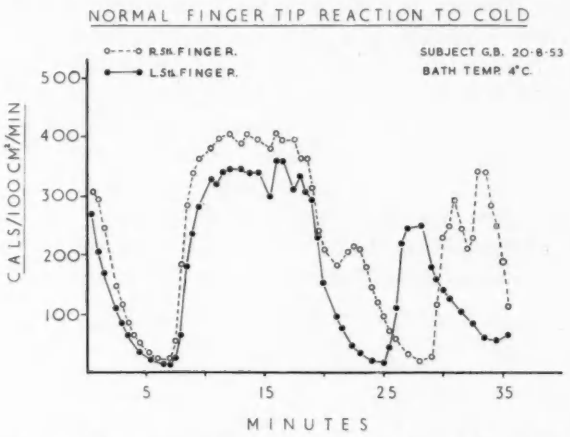


FIG. 3.—Normal finger-tip reaction to cold. Subject G. B., August 20, 1953. Both fifth fingers immersed at bath temperature 4° C., after preliminary immersion of both hands at 30° C. for 20 minutes.

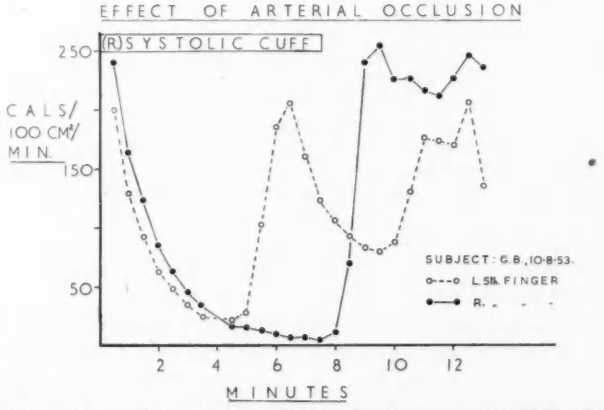


FIG. 4.—Effect of arterial occlusion. Subject G. B., August 10, 1953. Both fifth fingers immersed at bath temperature 5·3° C., after preliminary immersion of both hands at 30° C. for twenty minutes. At moment of immersion, circulation of right arm was occluded by an upper arm cuff, released after seven and a half minutes immersion. Closed circles: right fifth finger. Open circles left fifth finger.

at 5° C. heat elimination is initially high but falls rapidly during the first few minutes. Between five and ten minutes after immersion heat elimina-

tion rises, and successive waves of increased heat elimination occur during the period of test. It is probably correct (Greenfield and Shepherd, 1950) to interpret this increase of heat elimination as being due to vasodilatation in the finger-tips. The first part of the curve—for about the first six minutes after immersion—represents heat derived from the tissues of the finger cooling towards water-bath temperature. Fig. 4 compares the heat elimination curves of the fifth finger of opposite hands, the circulation of the right being arrested at the moment of immersion by a pneumatic cuff at a pressure of 200 mm. of mercury placed on the upper arm. Changes after this period represent alterations in blood flow.

As fig. 3 shows, the vasodilatation is about equal for both hands, though minor differences in the degree and in the periodicity of the waves of vasodilatation are to be seen. If (fig. 5) all fingers of one hand, and only

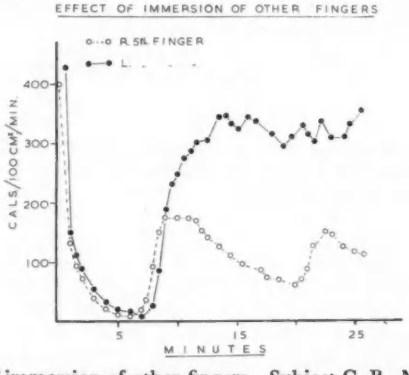


Fig. 5.—Effect of immersion of other fingers. Subject G. B., May 1, 1953. Right hand all fingers, left hand fifth finger only immersed at bath temperature 4° C., after preliminary immersion of both hands at 30° C., for twenty minutes. Closed circles: left fifth finger. Open circles: right fifth finger.

the finger under test of the other hand, are immersed the amount of vasodilatation in the former is considerably less than that in the latter. That heat elimination from all parts of the finger-tip is not uniform is shown in fig. 6 where rates of heat elimination from the finger pulps and from the dorsum of the distal segment are compared. Other experiments have shown a reduced rate of heat elimination from more proximal part of the finger-tip. To obtain some idea of the insulating effect of the finger-stall a thermo-couple was mounted on a cardboard tube at room temperature, a finger-stall applied over all, and the whole assembly immersed in the cold water-bath (fig. 7). Cooling was rapid during the first few minutes and after this the thermo-couple temperature attained moderate stability at a level of about 1° C. above that of the water-bath. When (fig. 8) a

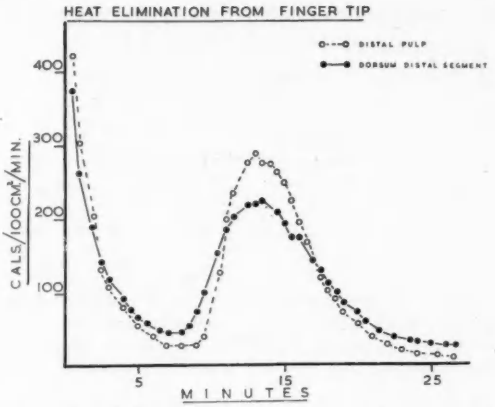


FIG. 6.—Comparison of heat elimination from palmar and dorsal aspects of finger-tip. Subject G. B., October 6, 1952. All fingers both hands immersed at bath temperature 4·8° C. after preliminary immersion both hands at 30° C. for twenty minutes. One heat disc on palmar aspect distal phalanx left index finger (open circles), one heat disc on dorsal aspect distal phalanx left index finger (closed circles).

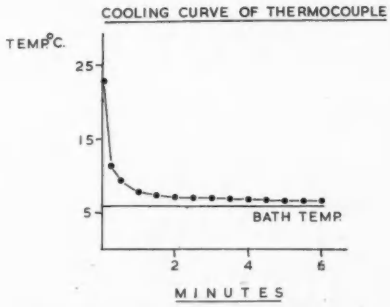


FIG. 7.—Cooling curve of thermocouple mounted on cardboard tube and covered with latex finger-stall, immersed at bath temperature 6° C.

thermo-couple is applied alongside a heat-flow disc to a finger under test, with no other insulation for the thermo-couple other than that provided by the finger-stall, the thermo-couple temperature is seen to fall to within 2° of bath temperature, and thereafter to reflect by minor temperature changes subsequent waves of vasodilatation. The actual temperature changes are not usually as large as those seen by Lewis (1930), in whose experiments the lagging of the thermo-couple junction (by three layers of adhesive strapping) was far more effective.

(2) *Observations on patients with peripheral nerve injuries.*—6 patients with peripheral nerve injuries were studied. 2 of these had a complete

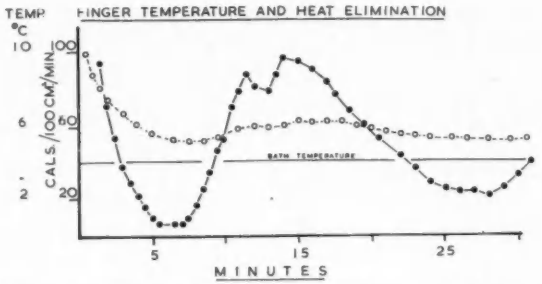


FIG. 8.—Comparison of finger temperature with heat elimination. Subject D. G., August 21, 1953. Both fifth fingers immersed at bath temperature 4° C. after preliminary immersion both hands at 30° C. for twenty minutes. Heat disc on pulp of right fifth finger (closed circles), with thermocouple alongside it (open circles).

division of the ulnar nerve (one 5 cm. above the medial epicondyle, the other in the lower third of the forearm), and one had a complete division of the median nerve 2 cm. above the wrist. The latter 2 patients, examined respectively 26 and 21 days after injury, showed (fig. 9) only a very small cold vasodilatation response when tested after preliminary immersion at

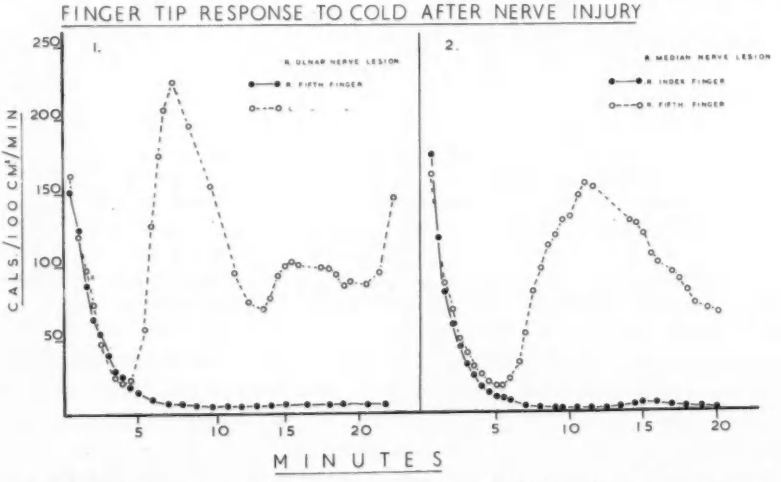


FIG. 9.—Response to cold after nerve injury. (1) right ulnar nerve lesion in lower forearm September 3, 1952. Tested September 29, 1952. All fingers both hands immersed at bath temperature 5° C. Closed circles: right fifth finger. Open circles: left fifth finger. (2) right median nerve lesion at wrist February 25, 1953. Tested May 18, 1953. All fingers right hand immersed at bath temperature 5° C. Closed circles: right index finger. Open circles: right fifth finger. Both tested after preliminary immersion both hands at 30° C. for twenty minutes.

30 ° C. The patient with complete division of the ulnar nerve at a point above the elbow was studied over a period of from nine days to six months after injury. The progressive change in the response over this period (fig. 10) is similar to that seen by Greenfield and his colleagues (1951)

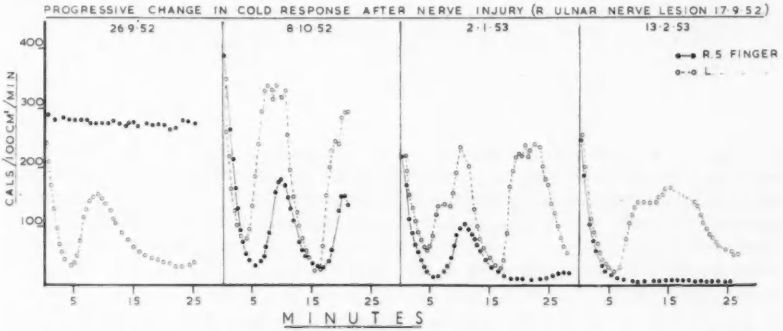


FIG. 10.—Progressive change in response to cold after nerve injury. Right ulnar nerve lesion 5 cm. above elbow September 17, 1952. Tested September 26, 1952, October 8, 1952, and June 2, 1953, after preliminary immersion both hands at 30° C. for twenty minutes, on February 13, 1953, after preliminary immersion at 20° C. for twenty minutes. In each case, bath temperature 5° C., all fingers both hands immersed. Closed circles: right fifth finger. Open circles: left fifth finger.

in observations on a similar patient. In the patient studied here the vasodilatation response was preserved throughout the period of the investigations, provided that the preliminary immersion was at 30° C. When a test was done at the fifth month after preliminary immersion at 20° C., the response of degeneration was seen.

In 2 other patients the ulnar nerve had been divided distal to the origin of the dorsal branch. Both showed a partial response after preliminary immersion at 30° C., heat loss from the anæsthetic fifth finger pulp being measured in each case.

In the sixth patient—who underwent resection and suture of a lesion in continuity of the median nerve on account of imperfect recovery—it was possible (fig. 11) to observe the return of the cold vasodilatation response occurring as recovery of sensibility took place.

(3) *Observations on the effect of pre-ganglionic sympathectomy.*—Cold vasodilatation responses were studied in 3 patients before and after pre-ganglionic cervical sympathectomy. The operation was in each case carried out through an anterior approach, the sympathetic chain being divided below the third dorsal ganglion, the rami of the second and third ganglia being divided and the chain being pulled up into the neck.

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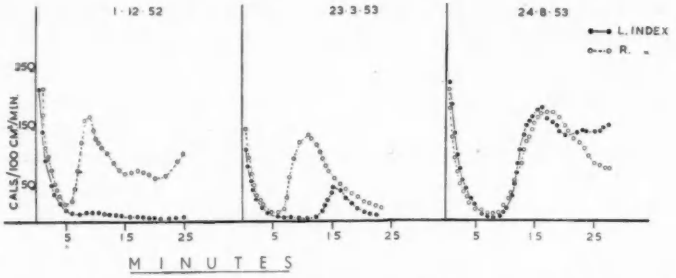

FIG. 11.—Progressive change in response to cold in patient who underwent resection and suture of left median nerve lesion on November 13, 1952. At the time of the latest test (August 24, 1953) there was practically complete sensory recovery. In each case, all fingers both hands immersed at bath temperature 5° C. after preliminary immersion at 30° C. for twenty minutes. Closed circles: left index finger. Open circles: right index finger.

Case 1.—R. B., a girl of 21 years, had suffered from residual partial paralysis of the right upper limb, and almost total paralysis of both legs as a result of acute anterior poliomyelitis contracted at the age of 18. She had severe circulatory disturbances—cyanosis, chilblains and ulceration—in the right hand. There was no evidence of primary arterial disease, both reactive hyperæmia (Lewis, 1949) and reflex vasodilatation responses (Lewis and Pickering, 1931) being normal. Cervical sympathectomy was done on October 2, 1952, and was followed by an excellent clinical result.

Case 2.—C. B., a man of 36 years, cut his right wrist with glass in April 1942, and showed evidence of division of the median nerve. Primary treatment by skin suture only was followed by nerve exploration on May 25, 1942, at which time the median nerve was found "constricted by scar tissue," and no repair was undertaken. No recovery occurring, further exploration was done in February 1943. The lesion was resected and nerve suture performed. A further resection and suture was done on April 6, 1948, and neurolysis was done on July 12, 1951. There was no recovery of sensibility or of motor power in the distribution of the median nerve. The development in 1951 of a severe Raynaud's phenomenon in the fingers of the right hand led to the performance (February 12, 1953) of a pre-ganglionic cervical sympathectomy.

Case 3.—F. G., a man of 21 years, sustained a lesion of his right median and ulnar nerves in January 1953 from gun-shot wound. At the same time his left arm was so damaged as to require amputation. Nerve suture in May 1943 was followed by partial recovery, though the later development of a causalgic type of pain and of circulatory disturbances brought him again under treatment in 1952. In this patient also evidence of primary arterial disease was absent, and reactive hyperæmia and the reflex vasodilatation responses were normal. Cervical sympathectomy on December 4, 1952, was followed by relief of pain and by improvement in the circulatory state of the hand.

In these 3 patients the post-operative cold vasodilatation responses were quantitatively similar (fig. 12), although only in 1 patient (Case 1) was the primary lesion confined to the motor nerves.

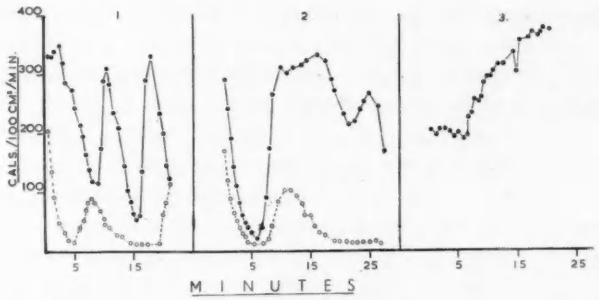

FIG. 12.—Response to cold after cervico-dorsal sympathectomy. 1 (*Case* 1), right sympathectomy October 2, 1953. Tested October 10, 1953. All fingers both hands immersed at bath temperature 5° C. after preliminary immersion both hands at 34° C. for twenty minutes. Closed circles: right fifth finger. Open circles: left fifth finger. 2. (*Case* 2), right sympathectomy February 12, 1953. Tested February 19, 1953. All fingers both hands immersed at bath temperature 5° C. after preliminary immersion both hands at 30° C. for twenty minutes. Closed circles: right fifth finger. Open circles: left fifth finger. 3 (*Case* 3), right sympathectomy December 4, 1952. Tested December 8, 1952. All fingers right hand immersed at bath temperature 5° C. after preliminary immersion right hand at 30° C. for twenty minutes. Closed circles: right fifth finger.

(4) *Observations on patients with traction lesions of the brachial plexus.*—13 patients with traction lesions of the brachial plexus were studied, in all of whom the paralysis was at first complete, and recovery, when occurring, of late appearance. The usual method of injury was by some sort of accident with a motor or pedal cycle, and all except one of the patients were males. The full plan of investigation included—besides clinical examination and motor and sensory charting—sweating test (White *et al.*, 1952), oscillometry, reactive hyperæmia test (Lewis, 1949), and reflex vasodilatation response (Lewis and Pickering, 1931). Finally, the cold vasodilatation response of the finger-tips and the cutaneous reaction of the forearm to histamine were studied. In 9 patients the brachial plexus was explored in order to obtain some idea of the prognosis from the gross appearance of the lesion. In the hope of making an accurate prognosis and in order to get the fullest possible information on the pathology of these lesions an exposure of the plexus rather more extensive than that previously employed was evolved during the course of these investigations. This exposure was obtained through a long transverse incision placed over the lower part of the neck. The cleidomastoid and omohyoid muscles were divided and, after division of the cervical fascia, the scalenus anterior muscle was defined, traced to its insertion and divided. After ligation of one or two upward running branches the subclavian artery was retracted downwards. By this means it was usually possible to display the whole

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plexus and to obtain a funicular biopsy from each trunk, or even from each root. In some cases, scarring of and around the scalenus anterior made part of the dissection rather tedious, and in one case scarring around the first dorsal root led to accidental opening of the pleura. No other hazards were encountered. In all the patients reactive hyperæmia was normal and in only one was the reflex vasodilatation response present; in none of the explorations was a motor response obtained to electrical stimulation of the plexus. In no patient at the time of latest examination was there any significant recovery of sensibility. It was not possible in all cases to apply the full plan of investigation. Table I records clinical findings in the 13 patients, together with the results of the investigations performed. Nine patients showed a positive axon reflex response, either to cold or to histamine.

Comparison of reflex responses with operative and histological findings (Table I).—This comparison is possible in 9 patients (Cases 1, 3, 4, 6, 7, 10, 11, 12, 13). In one patient (Case 1), in whom normal cold and histamine responses were present in all sites, the plexus appeared intact at operation, biopsy showing normal nerve structure in C.5 root,[1] and healthy myelinated fibres in C.6 root. In the patient (Case 3), with normal cold responses and absent histamine responses, exploration and biopsy showed, in the upper trunk, degeneration of all neural elements. In C.7 root there were degenerative changes but many unmyeliated and fine myelinated fibres were present, while C.8 root had been avulsed complete with the anterior and posterior roots of the nerve and contained many myelinated fibres. T.1 root showed normal nerve structure. Biopsy in the patient (Case 4), in whom normal cold vasodilatation was present in both index and fifth fingers and histamine response was positive on the ulnar side of the forearm, showed myelinated fibres and ganglion cells. Owing to considerable scarring, the root from which the biopsy was taken was difficult to place accurately, but it was probably C.7 root. In Case 6, with positive responses in the lower root distributions only (fifth finger and ulnar side of forearm), biopsy showed degenerative changes in roots C.5, 6 and 7, empty Schwann tubes in C.8 root, and normal myelinated fibres in T.1 root. The other patient (Case 7) with similar axon reflex responses, showed at exploration a post-ganglionic lesion of the upper trunk, roots C.7, C.8 and T.1 being in continuity as far proximally as the intervertebral foramina. Biopsy showed degeneration of neural elements in the upper three roots;

[1] Johnston and Willis (1946) state that "the brachial plexus is formed by the union of the anterior primary rami of the lower four cervical nerves . . . these nerves constitute the *roots* of the plexus." The term "root" is therefore used here in that sense. The qualification anterior or posterior is used to indicate the root of the nerve as distinct from the root of the plexus.

in the specimen taken from C.8 root numerous conducting elements were seen.

In 2 patients (Cases 10 and 13), both cold and histamine responses were absent. In the first of these, exploration clearly showed a post-ganglionic lesion of the upper trunk, C.7 and C.8 roots were much scarred and T.1 root was seen to be torn from the intervertebral foramen. The latter root was connected to the foramen by a meningocele. Biopsy showed no evidence of conducting elements in any of the roots. In the second patient (Case 13), exploration showed a complete rupture of the plexus about 2 cm. lateral to the intervertebral foramina. Biopsy showed complete absence of conducting elements. Finally, biopsy in the 2 patients (Cases 11 and 12) with absent cold responses failed to show any evidence of normal conducting elements.

These findings show that axon reflexes, if present, are always associated

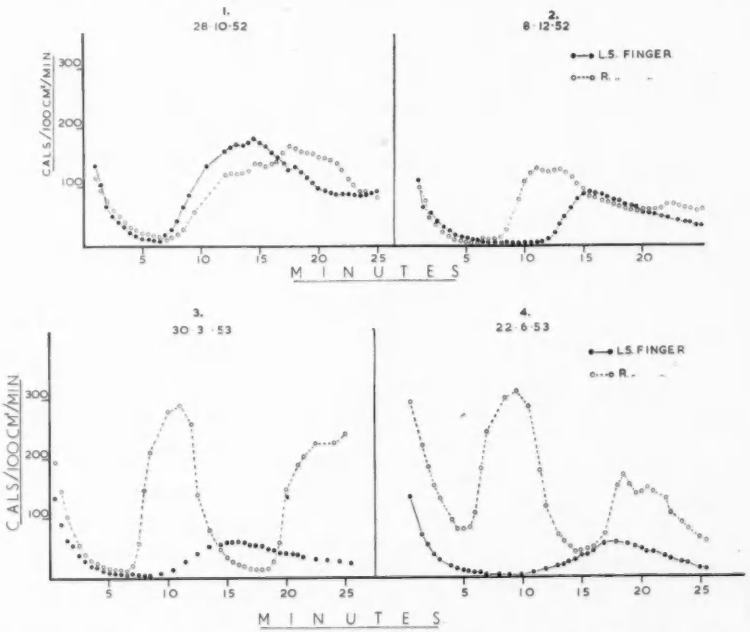

FIG. 13 (*Case* 3).—Progressive change in response to cold of left fifth finger following resection of C8 posterior root ganglion. (Left brachial plexus lesion July 7, 1952, operation December 11, 1952). Closed circles: left fifth finger. Open circles: right fifth finger. Tested on all four occasions at bath temperature 5° C. with all fingers both hands immersed. On October 28, 1952, after preliminary immersion at 30° C. for twenty minutes: on December 8, 1952, March 30, 1953, and June 22, 1953, after preliminary immersion at 20° C. for twenty minutes.

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TABLE I.—CLINICAL, OPERATIVE AND HISTOLOGICAL FINDINGS IN THIRTEEN CASES OF COMPLETE TRACTION LESION OF THE BRACHIAL PLEXUS

Case	Age	Date of lesion	Horner	Cold vaso-dilatation Index. 5th	Histamine Radial.	Histamine Ulnar	Exploration	Biopsy	Recovery
1 R. S.	13	9 Feb. 1950	+	+	+	+	*8 June 1950.* Plexus apparently normal	C.5 normal nerve structure C.6 many myelinated fibres	*June 1953.* Sensory: nil. Motor: triceps 2 F.D.S. 4 F.D.P. (Lat.) 3
2 J. M. D.	18	11 Aug. 1951	Pupil only	+	+	Not tested	Not performed	——	*July 1953.* Sensory: nil. Motor: P. major 4
3 A. S.	16	7 July 1952	+	+	+	–	–	*11 Dec. 1952.* C5/6 – hard lesion in continuity C7 – in continuity C8 – pulled out from cord T1 – in continuity	Degeneration conducting elements Many unmyelinated and some myelinated fibres Posterior root ganglion and myelinated fibres Normal nerve structure	*9 Sept. 1953.* Sensory: nil. Motor: P. major 4 Deltoid 1
4 J. Mc. P.	28	23 Aug. 1951	+	+	+	–	+	*20 Dec. 1951.* C5/6 hard lesion in continuity C7 – involved in above	Degeneration conducting elements Ganglion cells	*August 1953.* Sensory: nil. Motor: nil.
5 A. F.	30	6 Aug. 1952	+	+	+	–	+	Not performed	——	*September 1953.* Sensory: nil. Motor: P. major 3
6 D. H.	19	23 June 1952	+	–	+	–	+	*15 Jan. 1953.* C5/6 – hard lesion in continuity C7 – in continuity C8 – „ „ D1 – „ „	Occasional small fibres „ „ Empty tubes Normal nerve structure	*August 1953.* Sensory: nil Motor: nil

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7 B. L.	19	7 June 1953	0	−	+	−	+	*3 Sept. 1953.* C5/6 – hard lesion in continuity C7 – in continuity C8 – „ „ T1 – „ „	Degenerative changes „ „ Numerous conducting elements	*June 1954.* Sensory: nil Motor: nil
8 T. W.	9	5 Dec. 1952	+	−	−	−	+	Not performed	——	*December 1953.* Sensory: nil Motor: nil
9 T. A.	27	15 July 1947	+	Not done		−	+	Not performed	——	*May 1950.* Sensory: nil Motor: P. major 4
10 J. D.	18	19 Aug. 1951	+	−	−	−	−	*29 May 1952.* C5/6 – hard lesion in continuity C7 – in continuity C8 – „ „ T1 – torn out from i.v. foramen	No evidence conducting elements	*July 1953* Sensory: nil Motor: P. Major 3 Biceps 3 Triceps 2 Forearm flexors 1
11 B. J.	14	June 1950	+	−	−	Not done		*15 Feb. 1951.* Upper part of plexus probably lesion in continuity	C5/6 complete degeneration of conducting elements	*July 1953.* Sensory: nil Motor: Biceps 3 Deltoid 2 B.R. 1–2
12 A. T. B.	22	28 May 1951	0	−	−	Not done		*22 Nov. 1951.* C5/6 hard lesion in continuity	Degeneration of conducting elements	*August 1953.* Sensory: nil Motor: P. major 3
13 D. O.	24	22 Aug. 1953	Pupil only	−	−	−	−	*10 March 1954.* Plexus torn completely across	C5/6. No intact nerve bundles. No myelinated fibres	*April 1954.* Sensory: nil Motor: nil

\+ in relation to cold vasodilatation and histamine responses signifies a normal reaction.
\- an absent or grossly defective reaction.
Figures in column 9 signify M.R.C. grade of recovery.

with conducting elements which may be found on exploration and biopsy. They also make it possible to predict, from examination of axon responses, what will be the histological findings in individual roots. The findings in Case 6 provide further evidence on the latter point.

Case 6.—A. S., a lad of 16, was knocked off his bicycle by a car on July 7, 1952, and sustained a traction lesion of the left brachial plexus. When seen on August 27, 1952, at the Royal National Orthopædic Hospital, he had a motor and sensory paralysis of the left upper limb, the rhomboids only being spared. Cold vasodilatation tests (fig. 13 (1)) showed normal responses in index and fifth fingers, but the response to histamine was absent on the forearm. At exploration of the plexus (G.B.) five months after the initial injury, a lesion in continuity of the upper trunk was found; C.7 root was apparently undamaged, and C.8 root had been avulsed from the cord and was lying in front of the plexus in continuity with the anterior and posterior roots of the nerve. The posterior root had been torn at a point proximal to its ganglion. T.1 root appeared relatively normal as far proximally as the intervertebral foramen. Biopsy showed: in the upper trunk degeneration of conducting elements; in C.7 root many unmyelinated and fine myelinated fibres; in T.1 root an almost normal structure. C.8 root with its anterior and posterior roots was excised; section (fig. 14) showed the histological appearances of a posterior root ganglion, the structure of C.8 root itself being practically normal. Following this operative conversion of a pre-ganglionic to a post-ganglionic lesion, the cold vasodilatation response was examined (fig. 13 (2), (3), (4)) at intervals up to the sixth month after operation. The response of the left fifth finger, initially about two-thirds that of the right fifth finger, was reduced at the sixth month to less than one-fifth, while the response of the index finger had not altered. Eighteen months after the lesion, return of voluntary power in the pectoralis major (M.R.C. Grade 4) was the only improvement noticed.

Correlation of Reflex Findings with Subsequent Recovery

In 12 patients (all except Case 13) observation was continued for one year or more after injury.

3 to 4 years	2	(Cases 1, 11)
2 to 3 years	5	(Cases 2, 4, 9, 10, 12)
1 to 2 years	5	(Cases 3, 5, 6, 7, 8)

In none of these was there sensory recovery in the hand or lower two-thirds of the forearm.

Of the 3 patients (Cases 10, 11, 12) in whom no positive evidence of reflex activity was shown, 2 (Cases 10, 11) obtained a useful degree of motor recovery (Table I). The third (Case 12) at two and a half years had recovery only of the pectoralis major (M.R.C. Grade 3).

Of the remaining 9 patients (Cases 1, 2, 3, 4, 5, 6, 7, 8, 9) in whom reflex responses were elicited, only one (Case 1) showed a useful degree of motor recovery (Table I). The findings in this patient were so unusual as to warrant more detailed description.

Case 1.—R. S., a lad of 13, was on February 9, 1950, knocked off his bicycle by a lorry. He sustained multiple injuries, the chief of which was a traction lesion of

the right brachial plexus. At first no Horner's syndrome was evident, but its appearance was noted in March 1950. When seen at the Royal National Orthopædic Hospital on March 20, 1950, he had a motor and sensory paralysis of the right upper limb, with sparing only of the levator scapulæ. A cervical scoliosis, without evidence of bony injury, was present; screening of the chest showed a paralysis of the right diaphragm. At exploration on June 8, 1950 (Mr. H. J. Seddon), the brachial plexus was found apparently normal, without distortion or scarring. There was no motor response to electrical stimulation. Biopsy showed normal nerve structure in C.5 root and many healthy myelinated fibres in C.6 root. In May 1953 the extent of motor recovery was: triceps (M.R.C. Grade 2), flexor digitorum sublimis (M.R.C. Grade 4), lateral part of flexor digitorum profundus (M.R.C. Grade 3). There was no recovery of sensibility. At this stage, the cold vasodilatation response of the second and fifth fingers was normal (Fig. 15), and responses to histamine were normal on both sides.

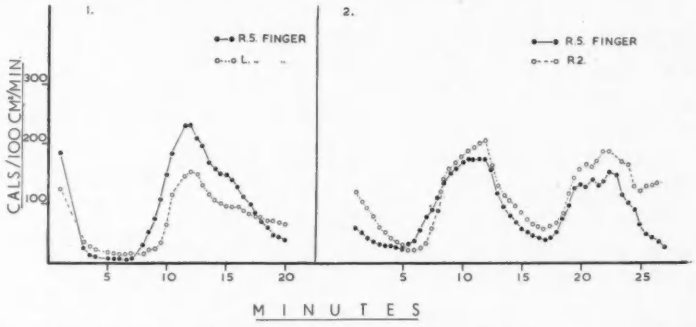

FIG. 15.—Response to cold in Case 1. (Right brachial plexus lesion February 9, 1950.) 1, Tested May 28, 1953. All fingers both hands immersed at bath temperature 4·3° C, after preliminary immersion both hands at 30° C. for twenty minutes. Closed circles: right fifth finger. Open circles: left fifth finger. 2, Tested May 29, 1953. All fingers right hand immersed at bath temperature 5° C. after preliminary immersion right hand at 20° C. for twenty minutes. Closed circles: right fifth finger. Open circles: right index finger.

of the forearm and of the dorsum of the hand. Further, a good rise in temperature of the affected fingers followed warming of the opposite upper limb, and pilomotor activity in the affected forearm could be elicited by stroking the back of the neck. A formal sweating test was not done, but light spontaneous sweating could be seen in all fingers of the affected hand.

This patient's lesion was almost certainly a very high one, in which pre-ganglionic damage was inflicted and the autonomic paths were spared. It illustrates the possibility of dissociation of the posterior from the anterior root lesion, since motor recovery in the distribution of C.8 root certainly occurred. The differentiation of such a case from the more usual types of pre-ganglionic lesion should be possible by examination of vasomotor and pilomotor activity—in this patient alone of the series the reflex vosodilatation test was positive and pilomotor and sudomotor activity was demonstrated in the affected limb.

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Discussion

(*a*) *Results in healthy subjects.*—These agree quite well with the results obtained by Lewis (1930) and by Greenfield and Shepherd (1950), and confirm that the method used here for estimating cold vasodilatation is—subject to two reservations—a valid one. The first reservation is, that the method of expressing results in calories/100 cm.^{2}/min. as if the rate of heat elimination from all areas of the finger-tip were uniform, is clearly inaccurate as it has been shown that this is not in fact so. The same objection is probably not valid against the comparison of heat elimination from opposite fingers, since the results show that heat elimination from comparable areas of opposite fingers is approximately the same. The second objection arises with relation to the figures for heat elimination obtained by the present method: though on one very hot day a rate of heat elimination of 400 calories/100 cm.^{2}/min. was observed, under ordinary circumstances the greatest rate of heat loss observed in these experiments in healthy fingers was in the range of 250–300 calories/100 cm.^{2}/min. Now the volume of the portion of finger immersed—representing a surface area of 22 cm.^{2} — was 7·5 c.c. A rough translation of cals./100 cm.^{2}/min. into cals./100 c.c./min. gives a maximum rate of heat elimination of 900 cals./100 c.c./min. — considerably lower than the figures of 1,100–3,400 cals./ 100 c.c./min. obtained by Greenfield and Shepherd (1950). Part of this difference is probably due to the insulating effect of the finger-stall: the other and larger part is due to the fact that the figures here were obtained by immersion of fingers in water at 5° C. as compared to Greenfield and Shepherd's starting temperature of 1° C. When a lower water bath temperature (2° C.) was used, rates of heat elimination (without general vasodilatation) of 450–500 cals./100 cm.^{2}/min. were observed representing values of 1,350–1,500 cals./100 c.c./min.

(*b*) *Results in patients with peripheral nerve injuries and in sympathectomized patients.*—The findings here simply afford confirmation for the work of Greenfield and his colleagues (1951), all the evidence supporting the hypothesis that the cold vasodilatation response depends largely on the integrity of the cutaneous axons.

Greenfield and his co-workers (1951) did not have the opportunity of observing the return of the cold vasodilatation response after successful nerve suture, and the present study provides some information on this point.

(*c*) *Results in patients with traction lesions of the brachial plexus.*—From the clinical and histological evidence presented here, it is clear that in many cases of traction lesion of the brachial plexus the damage is

proximal to the posterior root ganglion. To go further than this, and deduce from observed reflex findings the level of the lesion in individual roots, would require evidence regarding the root distribution of the plexus. Such evidence is in fact available from the observations recorded here. Thus, with regard to C.6 root; in the one patient (Case 1) with a normal histamine response on the radial side of the forearm, C.6 root was found to contain myelinated fibres. In all the other patients tested the histamine response on the radial side of the forearm was negative, and biopsy failed to show any conducting elements in the upper trunk. With regard to C.7 root: 2 patients (Cases 3, 4) showed a normal cold vasodilatation response in the index finger, linked with the finding of myelinated fibres in C.7 root. Regarding C.8 root: one patient (Case 3) showed a normal cold vasodilatation response in the fifth finger, linked with the finding of a pre-ganglionic lesion of C.8 root. A diminution of the cold vasodilatation response in the fifth finger followed operative resection of the C.8 posterior root ganglion. In the second patient (Case 6) where the fifth finger responded normally to cold, biopsy of C.8 root showed empty tubes, but the structure of T.1 root was normal. In the third patient (Case 7) whose fifth finger showed a normal response to cold, undegenerate fibres were demonstrated in C.8 root. Regarding T.1 root: one patient (Case 10) showed no response to histamine on the ulnar side of the forearm, linked with the finding of complete degeneration in T.1 root. A second patient (Case 7) showed a normal histamine response on the ulnar side of the forearm linked with the biopsy finding of myelinated fibres in T.1 root. The other patient (Case 3), in whom myelinated fibres were found in T.1 root, showed no response to histamine on the ulnar side of the forearm.

Failure to find myelinated fibres in the root supposedly supplying an area showing normal axon reflexes can, of course, be explained on the basis that funicular biopsy of a root removes only a small portion of that root for examination. It is probably justifiable to suppose that biopsy of another part of the root might show myelinated fibres. However, only in very exceptional circumstances is it justifiable to remove a whole root for examination. The absence of axon reflexes (as in Case 3) in an area whose supposed root of supply is shown to contain myelinated fibres cannot, however, be explained on this basis. With this reservation, and with the reservation that there is clearly considerable variation in root distribution, one may consider root distribution as:

Root C.6	Radial side of forearm.
Root C.7	Index finger.
Root C.8	Fifth finger.
Root T.1	Ulnar side of forearm.

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There is no evidence from the present work as to the root supply of the middle and ring fingers. This hypothesis differs only from that of Foerster (1933) with regard to the distribution of C.6 root. In Foerster's view this root supplies not only the radial side of the forearm but also the thumb and index finger. In support of the view expressed here, the case may be cited of a man who on January 6, 1953, underwent biopsy of a left cervical lymph node. On recovery from the anæsthetic, a partial paralysis of the left upper limb was noticed. When first seen on April 8, 1953, at the Royal National Orthopædic Hospital, he had a motor paralysis involving the spinati, deltoid, and biceps, with sensory loss in an area on the outer side of the upper arm and in a narrow band down the radial side of the forearm but not involving the hand or any of the digits. At exploration on May 14, 1953, it was found that a segment of the upper trunk, about 2 cm. long, had mistakenly been resected during the original operation. This case illustrates operative resection of C.5 and C.6 roots without any subsequent loss of sensibility in the digits, and supports the hypothesis that the cutaneous distribution of C.6 root does not extend below the wrist.

On this hypothesis of root distribution, it is possible by clinical examination and by examination of axon reflexes, to map out a lesion of the brachial plexus with regard to placing the damage of a given root as pre- or post-ganglionic. It would seem that pre-ganglionic damage more usually affects the lower roots—especially C.8 and T.1, while the lesion of the upper trunk is nearly always post-ganglionic. The evidence from the cases studied here does not support Jefferson's conclusion (1930) that intradural rupture is most common in the case of C.7 root, though on anatomical and mechanical grounds alone his conclusion would seem the more reasonable. More recently, White and Hanelin (1954) have presented myelographic evidence on this point, showing traumatic meningoceles in three patients with brachial plexus lesions. Of these, one showed meningoceles in relation to the seventh and eighth cervical intervertebral foramina, one in relation to the eighth cervical and first thoracic foramina, and one in relation to the fifth cervical intervertebral foramen. These workers relate the occurrence of a meningocele to an avulsion of roots from the cord. Their findings receive confirmation from the present work, since in one patient of this series a meningocele of the first thoracic intervertebral foramen was found at operation (Case 10). In a second patient (Case 9) there was presumptive evidence of an avulsion of the first thoracic root with the formation of a meningocele: in this patient, histamine responses on the ulnar side of the forearm were positive and—during an attempted paravertebral block—cerebrospinal fluid was withdrawn by needle puncture, the needle being introduced directly forward from a point 4

cm. from the mid-line between the first and second ribs. Unfortunately, too little is known of the exact mechanism of the injury in any of the present cases to justify any attempt at explaining the apparently greater liability of the lower roots to intradural damage. The evidence strongly supports Jefferson's conclusions with regard to the site of damage in C.5 and C.6 roots indeed, the frequent clinical finding of sparing of those muscles (rhomboids and serratus anterior) innervated by the most proximal branches of C.5 and C.6 roots is good evidence that the damage to these roots is commonly post-ganglionic. The present hypothesis would help to explain the common failure of sensory recovery and the equally common failure of motor recovery in peripheral muscles. Hitherto, failure of motor recovery has generally been considered as due to the distance of the affected muscle from the site of the lesion. By the time re-innervation occurred, changes in the muscle would be so profound as to render re-innervation useless. This explanation, however, would not suffice for the failure of sensory recovery, since return of sensibility is not subject to the same time limitations as is return of motor power. Return of sensibility has been seen when the median nerve has been sutured as long as thirteen years after the original denervation. According to the hypothesis presented here, sensory recovery would fail on account of the pre-ganglionic nature of the lesion. The common failure of recovery in the peripheral musculature would be explained by the occurrence of an intra-dural lesion affecting the lower roots of the plexus.

The question now arises how much such findings may be of help in prognosis, for early appreciation of a hopeless prognosis is of great help in dealing with these lesions, enabling reconstruction to be proceeded with and saving months of useless physiotherapy. Certainly, previous observations have shown that plexus exploration itself may be an unreliable guide except in the rare event of a complete rupture of all elements (as in Case 13). The prognostic significance of axon reflexes is clearly subject to three reservations: Firstly, the demonstration or otherwise of axon reflexes depends only on changes occurring in the posterior root system—it is quite possible (as indeed Case 1 shows) that a pre-ganglionic lesion of the posterior root may be combined with a recoverable lesion of an anterior root, though as the evidence here suggests, such an occurrence is unlikely. Secondly, the demonstration of axon reflexes in a given area need not necessarily mean that the whole of that root has been subjected to a pre-ganglionic lesion. Again, the evidence suggests that such an occurrence is unlikely. Thirdly, the demonstration of absent axon reflexes, though indicating a lesion distal to the intervertebral foramen, gives no evidence as to the severity of such a lesion. As such findings seem usually to

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relate to the upper trunk, with whose recovery we are chiefly concerned, prognosis may still be in doubt. However, it should be added that even operative exploration frequently fails to resolve this point. Certainly, examination of axon reflexes will often resolve the ambiguity of the operative finding of roots in continuity and relatively unscarred as far proximally as the intervertebral foramen.

Perhaps all that can justifiably be stated at this stage is that of 4 patients in whom axon reflexes were absent, 2 gained a useful degree of recovery. In one patient (Case 13), in whom all axon responses were absent, exploration showed a complete rupture of all elements of the plexus and no further "expectant" treatment was undertaken. This was, however, the only instance of such a finding in the present series. Of the 9 showing axon responses, only one—and that a most unusual case whose differentiation from the others was clinically possible—gained any useful degree of recovery.

Summary

(1) An investigation is described in which axon reflexes (cold vasodilatation and histamine responses) have been studied in patients with complete traction lesions of the brachial plexus. Where possible, clinical and reflex findings have been related to findings at exploration and biopsy.

(2) The validity of the technique used for testing the cold vasodilatation response has been proved by its application to healthy subjects and to patients with known peripheral nerve injuries.

(3) The results suggest: (*a*) That two types of brachial plexus lesion exist—pre-ganglionic and post-ganglionic—the pre-ganglionic type more commonly affecting the lower roots of the plexus.

(*b*) That the techniques used here may indicate the peripheral distribution of the several roots of the plexus and facilitate localization of a pre-ganglionic lesion to a particular root.

(*c*) That these findings explain the common failure of sensory recovery and the equally common failure of motor recovery in the more peripheral muscles.

(*d*) That examination of axon reflexes in conjunction with ordinary clinical methods may afford an idea of prognosis at least equal in value to that afforded by operative exploration.

Acknowledgments

I would like to thank Miss D. B. Gee who assisted me in all the experiments and in preparing the clinical records, and Dr. H. Sissons who undertook all the histological work involved. The investigation was undertaken at the instance of Mr. D. M. Brooks to whom I am most grateful for

PLATE XV

To illustrate article by George Bonney.

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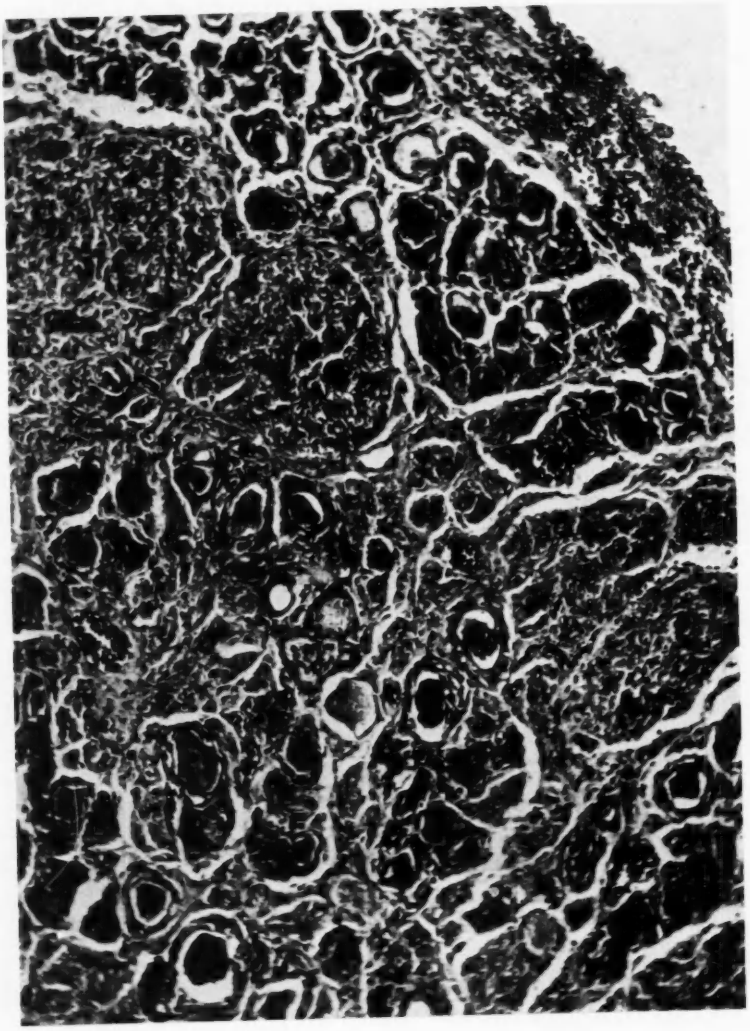
PLATE XVI



To illustrate article by George Bonney.

suggestions and for guidance in the operative and clinical work. My thanks are due to Mr. H. J. Seddon for his advice, encouragement and most helpful criticism: all the cases investigated were under his care at the Royal National Orthopædic Hospital, and I am most grateful to him for giving me the opportunity to examine them.

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LEGENDS TO PLATES

PLATE XV

FIG. 2.—Histamine responses of forearm in case of traction lesion of the brachial plexus (*Case* 6, D.H., lesion June 23, 1952, date of test January 12, 1953). Showing positive response on ulnar side of forearm, negative response on radial side. Both areas of skin completely anæsthetic.

PLATE XVI

FIG. 14 (*Case* 3).—Photomicrograph (Dr. Hubert Sissons) showing appearance of posterior root ganglion in the specimen of C.8 root removed at exploration of the brachial plexus December 11, 1952.

RECURRENT CONVULSIVE SEIZURES AS A SEQUEL TO CEREBRAL INFARCTION: A CLINICAL AND PATHOLOGICAL STUDY

BY

PHILIP R. DODGE, EDWARD P. RICHARDSON, JR.
AND MAURICE VICTOR

(From the Departments of Neurology and Pathology (Neuropathology), Massachusetts General Hospital, and the Department of Neurology, Harvard Medical School, Boston, Massachusetts)

INTRODUCTION

THE occurrence of focal and generalized convulsions during the acute phase of cerebral infarction in adults has been recognized for many years. Well-recorded clinical observations on the form and general frequency of such seizures are to be found in the writings of Jackson (1931) and Gowers (1901), among others. It has also been known that a certain number of patients, after recovering partially or wholly from the paralytic effects of an apoplectic attack, then have recurrent convulsive seizures. Unfortunately, there are only meagre pathological data as to the nature and location of the cerebral lesions responsible for this form of convulsive disorder. In fact, considering the magnitude of the medical literature on the subjects of epilepsy and cerebral vascular disease, it is surprising that few pathologically verified cases of epilepsy following cerebral infarction and hæmorrhage have been reported (Table II).

We do not believe, however, that this is a rare condition. In a recent statistical study of a year's case material from the Massachusetts General Hospital, we have found that convulsive seizures accompanied or followed cerebral infarction or hæmorrhage in 13 (12·5 per cent) of 104 consecutive autopsy-proven cases; and 6 (5·8 per cent) of the 104 patients suffered from recurrent seizures, that is, epilepsy (Richardson and Dodge, 1954). The present report is concerned with an analysis of the clinical and pathological data from 6 cases in which epilepsy appeared to develop as a consequence of cerebral infarction. Our purpose in doing this is to call attention to an important and often overlooked cause of recurrent seizures in adult life.

Case I.—M.G.H. 718582.

A 75-year-old woman with angina pectoris and auricular fibrillation developed episodic paresthesias in the left upper arm, and then had generalized convulsive seizures in the last four years of her life. There was no definite apoplectic episode. Post-mortem examination disclosed a small solitary old infarct in the "arm" area of the right postcentral gyrus.

The patient, a 75-year-old white woman, was admitted to the Massachusetts General Hospital for the first time on October 26, 1950, because of increasing lassitude, dyspnœa, and minimal ankle œdema. She had been subject to occasional attacks, lasting a few seconds, of sharp, severe substernal pain which radiated at times into one or both arms. All other cardiac symptoms were specifically denied.

On this admission she reported an episode of abnormal sensation in the left arm which had occurred about four years before. This she described graphically as a sudden "drawing, sickening sensation" along the posterior aspect of the left upper arm, which lasted a few minutes. Six months later she had a similar attack. In addition she reported six episodes of loss of consciousness, not further described, which lasted from twenty minutes to twenty-four hours. These occurred during the three or four years prior to admission.

Early seizures, head trauma and a family history of convulsive disorder were denied.

On physical examination she did not appear ill. There was minimal retinal arteriosclerosis. The blood pressure was 125 systolic, 70 diastolic; the pulse-rate was 90 per minute and totally irregular. The heart was enlarged to the anterior axillary line, and there was a loud apical systolic murmur. No diastolic murmur was heard. There were signs of a right hydrothorax. The liver edge was felt four fingerbreadths below the right costal margin. Neurological examination was reported as negative. An electrocardiogram showed auricular fibrillation, and a chest roentgenogram confirmed the presence of a right pleural effusion. The pleural fluid was subsequently removed by thoracentesis. She was treated with a low salt diet, digitoxin 0·1 mg. per day, and was discharged from the hospital on November 6, 1950.

During the subsequent year she had attacks of unconsciousness with total amnesia lasting from several hours to three days. These occurred about once or twice a month. She was said to "froth at the mouth," but a clear history of convulsive movements was not obtained. On at least two occasions these attacks were preceded by a sensation of "heaviness" in the ears, nausea, and a feeling of "whirling." Meanwhile there was a mild increase in symptoms and signs of congestive failure.

On April 18, 1952, she was admitted to the Neurological Service after an attack of unconsciousness. On the preceding day, her family had found her lying in bed in an unresponsive state, in which she remained for the next twelve hours. During this period, she rolled about in bed and picked at the bedclothes. She then regained consciousness, but was confused and belligerent. When brought to the hospital about ten hours later, she was agitated, combative, and disoriented, and would not permit adequate examination, but there were no obvious paralyses and the tendon reflexes were active and equal. She left the hospital against advice before further investigations could be carried out. On April 22, 1952, she was admitted to the Surgical Service after another similar attack during which she had struck the left forehead and right arm. Examination revealed a contusion of the left forehead, and a Colles fracture of the right wrist. There was mild confusion, but the neurological examination was otherwise negative. On lumbar puncture the cerebrospinal fluid pressure was equivalent to 98 mm. of water; the fluid contained no cells, and a total protein of 39 mg. per cent. An electroencephalogram on April 23, 1952, showed generalized low and medium voltage slow activity, with paroxysmal bursts of 2–3 per second activity. Meanwhile the confusion cleared and on April 24, 1952,

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she was described by a psychiatric consultant as "lucid, co-operative and well oriented in all spheres, pliable, and willing to follow recommendations." Skull roentgenograms were negative. She was discharged on May 1, 1952. She always presented a difficult problem in therapy, as she followed her cardiac regimen poorly, and failed to take her recommended anticonvulsant medication.

On June 16, 1952, the patient had a sudden brief generalized convulsive seizure, followed in fifteen minutes by another similar seizure. She was immediately brought to the hospital; a third generalized seizure occurred at the time of admission. On examination, she was comatose with bilateral extensor plantar reflexes, but no other definite neurological abnormalities were found. There was auricular fibrillation with a pulse deficit of about 20. The blood pressure was 138 systolic, 86 diastolic. She had another generalized seizure during the night. Over the next four days she recovered consciousness, the plantar reflexes became flexor, and she was discharged home.

The final admission was on August 11, 1952, again after two generalized seizures. While being examined in the admitting ward she had a generalized convulsion, during which respirations ceased, and she died shortly thereafter.

Pathological Findings (*M.G.H. Autopsy No.* 15,678).

General: Autopsy was performed fourteen hours after death. There was bilateral hydrothorax, and marked pulmonary congestion and œdema. The heart weighed 430 grammes, and appeared generally dilated. The left ventricular wall was 18 mm. thick, and there was slight patchy endocardial fibrosis. The valves appeared normal and no mural thrombus was found. There were minimal coronary and slight aortic atherosclerosis, and moderate nephrosclerosis. The liver showed minimal gross and microscopic evidence of passive congestion.

Neuropathological findings: The brain weighed 1,350 grammes. The large arteries at the base of the brain showed only minimal atherosclerosis, and no occluded vessels were seen. On external examination the only abnormality noted was a small (1·0 x 0·8 cm.) depressed lesion located in the post-central gyrus about 3 cm. above the Sylvian fissure. The leptomeninges were intact over this area and not adherent to the dura mater. Cuts through the lesion (fig. 1A) disclosed that it consisted of a sharply demarcated focus of destruction of cortex and adjacent white matter to a maximum depth of about 2 cm.

The microscopic appearance of the lesion was typical of old infarction. Its centre consisted of an irregular cavity traversed by numerous fine strands of collagenous connective tissue and small blood vessels (fig. 1B). A few macrophages, some of them containing blood pigment, were enmeshed within this network. The cerebral cortex overlying the lesion was absent and, in its place, the pia-arachnoid was fused with the connective tissue network within the cavity. In the surrounding brain at the edges of this cavity, there was a partial loss of cortical nerve cells, and astrocytes were increased in size and number. The location of the lesion in the post-central gyrus was confirmed by the microscopic sections (fig. 5A). The examination, gross and microscopic, of the remainder of the brain was unremarkable except for the presence in the cerebral cortex of a moderate number of "senile plaques." Neurofibrillary changes in neurones were rare.

Comment.—The cerebral infarct in this case is consistent in age with the onset of neurological symptoms about five years prior to death. Its small size explains the absence of abnormal neurological findings, and its position in the post-central gyrus provides an explanation for the discrete sensory symptoms in the left upper arm. The initial attack may have represented the apoplectic incident itself or, alternatively, may have been

a limited sensory seizure arising from a focus near the infarct. The short duration and the recurrence of this symptom on at least one occasion would favour the latter interpretation. Subsequent seizures were, for the most part, poorly described but appeared to be generalized and associated with prolonged post-ictal confusion. The diffuse pathological changes of senile dementia may have increased the patient's susceptibility to seizures or accounted for the severe after-effects, although it is of interest that psychiatric examination not long before death showed a striking lack of evidence of dementia. A source for emboli was not discovered at autopsy; but the patient was known to have suffered from auricular fibrillation, and it seems probable that the left auricular appendage at one time contained a mural thrombus which subsequently formed an embolus.

Case II.—M.G.H. 425304.

A 69-year-old man who seven years previously had suffered a myocardial infarction suddenly developed aphasia and weakness of the right face and arm. Ten days later he had the first of a series of convulsive seizures, both focal and generalized. Despite recovery from the initial neurological disability, the seizures recurred at frequent intervals until death, two years afterward, from embolism of the superior mesenteric artery and gangrene of the bowel, in association with auricular fibrillation. Post-mortem examination disclosed a large old cerebral infarct in the opercular portion of the left frontal lobe.

The patient, a 69-year-old white man, was admitted to the Massachusetts General Hospital for the first time on October 19, 1943, with the history of a dull, steady chest pain which had occurred seven days before admission and had lasted several hours. There was some radiation of pain into the left arm. He was said to have had hypertension ten years before but on admission to the hospital the blood pressure was 138 systolic, 78 diastolic.

The physical examination was unremarkable. An electrocardiogram was interpreted as consistent with a recent anterior myocardial infarct and an old posterior myocardial infarct. The chest roentgenograms showed an increased transverse diameter of the heart due mainly to enlargement of the left ventricle, increase in the pulmonary vascular markings and a generalized haziness which suggested pulmonary œdema. The sedimentation rate was elevated. The patient was virtually asymptomatic during his hospital stay and was discharged home on October 30, 1943. There were no neurological symptoms or signs.

On November 2, 1948, he was readmitted and successfully treated for a recurrent perineal abscess. He denied further cardiac symptoms at this time but reported that for the previous three years he had been treated for mild diabetes mellitus. This was well controlled with diet alone. The blood pressure was 160 systolic, 80 diastolic. Again there were no neurological symptoms or signs.

On January 10, 1950, he was admitted for the third time because of the sudden development, on the day before, of confusion and difficulty in speaking. On examination, the blood pressure was 170 systolic, 70 diastolic. The heart was enlarged to the left anterior axillary line. There were no murmurs. On neurological examination he was confused and dysphasic, answering "yes" to every question. There were nystagmus on lateral gaze to the right, weakness of the right lower face and deviation of the protruded tongue to the right. The right arm and hand were very slightly weak. The tendon reflexes were active and equal, and the plantar reflexes were flexor. Sensory examination was unsatisfactory. On lumbar puncture, the cerebro-

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spinal fluid pressure was equivalent to 150–160 mm. of water; the fluid was pink and contained 5,000–6,000 red cells per c.mm. and a total protein of 130 mg. per cent. Serological tests for syphilis on blood and cerebrospinal fluid were negative. The urine had a specific gravity of 1·020 and contained acetone, albumin, a large amount of sugar, and rare white blood cells. The fasting blood sugar was 197 mg. per cent. Blood counts were not remarkable. Confusion increased during the first few hospital days. On January 12, 1950 an electroencephalogram showed depressed voltages in the left temporal region and, to a lesser extent, in the left parietal region. Skull roentgenograms disclosed a 5 mm. displacement of the calcified pineal body to the right. A second lumbar puncture on January 13, 1950, showed a cerebrospinal fluid pressure equivalent to 40 mm. of water; the fluid was pink, and after centrifugation the supernatant fluid was xanthochromic. It contained 2,300 red blood cells per c.mm. and a total protein of 130 mg. per cent. On the same day a left temporal burr hole exploration was negative.

There was no significant change during the post-operative period until January 19, 1950, when he had a convulsive seizure. This began with bilateral twitching movements of the mouth and eyes, and chewing movements of the jaw. The head and eyes deviated to the right. After about three minutes, during which the patient was unresponsive, the seizure ceased, and the head and eyes returned to the mid-position. On January 20, 1950, he had a generalized convulsion during which the head and eyes were turned to the right. This lasted about seven minutes and was followed a few seconds later by a focal fit in which the head and eyes turned to the right and the right hand shook. This also lasted about seven minutes.

On January 21, 1950, he had another seizure. This began with a groan which was followed immediately by trembling of the lower jaw, rolling of the eyes, and then chewing movements of the jaws. The attack lasted about six minutes. An exactly similar seizure was observed the next day. He was treated with phenobarbital and diphenylhydantoin. The spinal fluid gradually returned to normal, the neurological signs improved, and he was ambulatory and rational on leaving the hospital in February 1950.

When next examined on October 23, 1950, no abnormal neurological signs could be elicited. He had continued to have seizures about once every three months, lasting one to two minutes; during one he fractured the third lumbar vertebra. His wife described the seizures as beginning with deviation of the eyes to the right, followed by generalized shaking of all limbs, the right more than the left. Consciousness was lost during the seizures. On November 5, 1951, an electroencephalogram showed generalized abnormality characterized by many high amplitude slow waves (7–8 per second), with occasional 1·5 per second waves over the right temporal region and at times over the left side of the head.

On February 28, 1952, he was admitted because of an episode of hæmatemesis, the cause of which was not found. Auricular fibrillation was suspected on physical examination, but the cardiac rhythm had reverted to normal by the time an electrocardiogram was done. On March 5, 1952, he was again found to have auricular fibrillation. On this occasion he was agitated, confused, and disoriented. No seizure was observed. He improved within twenty minutes except for slight weakness of the right face and hand, from which he recovered within a day. He was discharged to his home on March 20, 1952.

On June 12, 1952, he was admitted for the final time, because of abdominal pain. Since the previous admission he had had five seizures similar in type to the earlier ones. He died on July 4, 1952, four days after resection of gangrenous cæcum and terminal ileum.

Pathological Findings (*M.G.H. Autopsy No.* 15,590).

General: Autopsy was performed seven hours after death. A firm red-brown

thrombus was found in the superior mesenteric artery. There was bilateral fibrocaseous pulmonary tuberculosis and bilateral bronchopneumonia. The heart was enlarged, weighing 490 grammes. The apex of the left ventricle was markedly thinned and fibrotic, measuring 3 mm. in thickness; microscopically, it was composed entirely of collagenous connective tissue. Firmly adherent to the endocardium beneath this area was a large (4 × 3 × 1·2 cm.) mural thrombus, to the surface of which was loosely attached a dark red friable thrombus of more recent appearance. The coronary arteries were severely atherosclerotic, and the lumens were reduced to a pin-point diameter in many places. There was a severe degree of atherosclerosis of the aorta, especially of the abdominal portion, where several small dark-red thrombi were attached to intimal ulcerations. There were multiple recent and old infarcts in both kidneys and in the spleen.

Neuropathological findings: The brain weighed 1,250 grammes. The large arteries of the carotid and basilar systems were markedly atherosclerotic, but no occluded vessels were found. On external examination a large (3·5 × 3·5 cm.) depressed yellowish area of cortical destruction was visible in the left middle frontal convolution. This extended posteriorly into the opercular region. The pia-arachnoid overlying it was slightly adherent to the dura mater. On coronal section (fig. 2A) the lesion extended inward to involve the insula, external capsule, claustrum, lateral part of the anterior limb of the internal capsule, and lateral part of the putamen. Several small depressed foci of cortical destruction, similar in appearance to the large lesion, were found in the left occipital, right occipital, right frontal and left frontal regions. The brain-stem and cerebellum were normal.

On microscopic examination the lesions were consistent with resolving infarction. The destroyed brain tissue was replaced by a fine meshwork of collagenous connective tissue and capillaries (fig. 2B). Embedded in this and lying free in the adjacent brain substance, were numerous macrophages, many of which contained blood pigment. In the brain tissue surrounding the cavitation, there was pronounced reactive astrocytic gliosis. In addition, there were many microscopic lesions scattered throughout the cerebral cortex; these were characterized by destruction of nerve cells, and reactive astrocytic hyperplasia. The brain-stem and cerebellum were normal. Silver stains of the cerebral cortex revealed none of the changes characteristic of Alzheimer's disease.

Comment.—The location and appearance of the large lesion in the left cerebral hemisphere can be correlated with the apoplectic episode which occurred two and a half years before death. The finding of the blood pigment in the lesion indicates that the cerebral infarction was originally (at least in part) hæmorrhagic. This fact, and the presence of a mural thrombus in the left ventricle, would strongly favour embolic arterial occlusion as the basis for the cerebral lesion rather than locally developing thrombosis—even though there was severe atherosclerosis of the cerebral arteries. The seizures, first appearing ten days after the "stroke," had focal aspects consistent with a discharging lesion in the left frontal lobe. It is of interest to note that recurrent convulsive seizures were the only significant residual symptoms from the apoplectic attack.

Case III.—M.G.H. 771922.

A 47-year-old man, who suffered intermittent claudication and angina pectoris following an old myocardial infarction, suddenly developed episodic attacks of paræsthesia and involuntary jerking of the right leg about six months before his

death. In ensuing months the attacks increased in frequency and severity, spread to include the right arm and right side of the face, and were followed by increasingly prolonged periods of weakness of the right limbs, and by dysphasia. Death occurred a few hours after pneumoencephalography. Post-mortem examination revealed old thrombosis of the left internal carotid artery and recent thrombosis of both anterior cerebral arteries. In addition to extensive recent infarction of both cerebral hemispheres, there were several small, old infarcts predominantly in the left sensorimotor cortex.

The patient, a 47-year-old white man, was admitted to the Massachusetts General Hospital for the first time on April 15, 1952, because of recurrent attacks of weakness, numbness and jerking of the right leg over a seven-week period. The first attack, seven weeks before admission, began with a feeling of heaviness and numbness in the right leg, which he noticed on arising in the morning. The right leg collapsed under him and he fell to the floor, but then recovered almost immediately. In the ensuing weeks he had three attacks which were similar except that on those occasions there was uncontrollable jerking of the right leg with flexion movements at the knee and hip. These episodes lasted about two minutes. He had an occasional headache over the left eye during these seven weeks. For four years, he had had attacks of angina pectoris. For five to seven years he had suffered from recurrent aching in the calves on walking. He denied any past history of seizures or other significant neurological symptoms.

On physical examination the blood pressure was 160 systolic, 90 diastolic; the popliteal, posterior tibial, and dorsalis pedis pulses were not palpable and the feet felt cool to the touch. The neurological examination was normal except for minimal clumsiness of the right hand and questionable impairment of discriminative sensation over the dorsum of the right hand. Skull roentgenograms and the cerebrospinal fluid were normal. Serological tests for syphilis on the blood and cerebrospinal fluid were negative. An electrocardiogram was interpreted as suggestive of an old posterior myocardial infarction. An electroencephalogram revealed diffuse 4–6 per second slow activity over the entire left hemisphere. He was discharged on April 17, 1952.

During the next three months he experienced an increasing number of seizures, up to one or two a day, characterized by a tingling sensation beginning in the right leg, then extending upward on the right side to involve the trunk, arm, and, at times, the face. In these attacks, there was twitching of the right foot and at times of the right hand, weakness of the right limbs, and inability to speak. These lasted from one to ten minutes. During these three months the patient was described by his wife as unstable, depressed and forgetful. She noticed that from time to time he had difficulty in finding words and tended to stammer.

He was readmitted on July 22, 1952. On examination, he was slightly confused, hesitant in using words, and had extreme difficulty writing and reading. He was unable to subtract sevens serially from 100 but could retain 7 digits forward and 4 backward. The right pupil was slightly larger than the left. The right arm and leg were weak and clumsy. The tendon reflexes were slightly more active on the right side, and the right plantar reflex was extensor. There was a defect in ability to recognize number writing and estimate weights in the right hand. A second electroencephalogram was normal save for reduction in the amplitude of the alpha rhythm in the left occipital region. The cerebrospinal fluid again was normal except for an increase in the total protein from 43 mg. per cent (on the previous admission) to 56 mg. per cent. He was discharged on July 25, 1952.

He was admitted for the final time on July 29, 1952, and on the following day a pneumoencephalogram was performed. He tolerated the procedure poorly, became increasingly drowsy, and three hours later was unresponsive, with a complete right hemiplegia, weakness of the left limbs, and bilateral extensor plantar reflexes.

The left internal carotoid artery was observed to pulsate less on palpation than the right. The pneumoencephalogram showed slight generalized dilatation of the ventricular system. The patient had no further seizures but expired on August 2, 1952.

Pathological Findings (*M.G.H. Autopsy No.* 15,661).

General: Autopsy was performed within seven hours after death. There was moderate pulmonary congestion and œdema. The coronary arteries were greatly narrowed by severe atherosclerosis, and there was moderate atheromatous infiltration of the aorta. Examination of the heart showed focal myocardial fibrosis. Gross and microscopic study of the other organs disclosed no other significant abnormalities, except in the brain.

Neuropathological findings: The brain weighed 1,520 grammes. The dura mater and leptomeninges were unremarkable. There was marked atherosclerosis of the major cerebral arteries, particularly of the internal carotid arteries and their branches. The entire intracranial portion of the left internal carotid artery was completely occluded by firmly adherent light yellowish brown material, typical of old thrombosis. Both anterior cerebral arteries were filled with adherent dark reddish-brown blood clots, beginning on the right in the most proximal part of the artery, and on the left immediately beyond the anterior communicating artery. On the convex surface of the left parietal lobe there were multiple, small, depressed lesions characterized by focal destruction of cerebral cortex, typical of old infarction. Both cerebral hemispheres were extensively softened in a manner characteristic of recent infarction, with involvement of the frontal lobes bilaterally and of the superior portion of the temporal lobe and the region of the central fissure of Rolando on the left. There was bilateral herniation of the uncus and medial portion of the hippocampal gyrus through the tentorial opening, with multiple small fresh hæmorrhages in the tegmentum of the mid-brain and pons.

Microscopic examination of the areas of recent infarction showed disappearance, or shrinkage and pyknosis, of nerve cells, severe degenerative changes of the glia and necrosis of small blood vessels, and a moderate to marked degree of infiltration of the necrotic tissue by polymorphonuclear leucocytes. Myelin sheaths were still visible in the white matter, but were much more pale with Loyez staining than normal. In the left frontal and parietal regions, there were in addition scattered old lesions, 0·2 to 3 mm. in diameter, situated in the cerebral cortex. The largest of these was in the precentral gyrus, about 1 cm. lateral to the interhemispheric fissure (fig. 3A). Three others nearly as large were located in the inferior parietal lobule. The smallest lesions were in the frontal and posterior parietal regions. In all of them there was necrosis of the brain parenchyma with dense accumulations of macrophages. The blood vessels within the lesions showed endothelial proliferation, and surrounding the lesions astrocytes were greatly increased in size and number (fig. 3B). The appearance of the more extensive necrosis was consistent with a duration of twenty-four to forty-eight hours, whereas the cellular reaction in the small lesions indicated that these were at least several weeks or possibly several months old. Sections of the left internal carotid artery showed extensive atheromatous degeneration of the walls. The lumen of the upper three-fourths of the intracavernous portion of the artery was occluded by an old thrombus in which extensive recanalization and fibrous tissue organization had occurred, whereas the lumen of the lower fourth of this part of the artery was filled with more recent thrombus in which active organization and recanalization were taking place. In a section from the left parietal region, a small (0·2 mm.) branch of the middle cerebral artery contained an extensively recanalized thrombus. Very recent thrombosis, with no organization, was found in the occluded portions of the anterior cerebral arteries.

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Comment.—It seems most probable that the recurrent focal seizures were due to a discharging focus in the left sensorimotor cortex. Post-mortem examination disclosed severe cerebral atherosclerosis with old thrombosis of the left internal carotid artery and several small resolving infarcts in the left frontal and parietal regions, undoubtedly the result of the thrombosis. It might be argued that the seizures were produced by recurrent transient attacks of cerebral ischæmia due to impaired blood supply because of the carotid occlusion, and that they were not dependent upon the presence of demonstrable cerebral lesions. In this connexion, it is of interest that the seizures began in the leg, for which the cortical area is situated in the most remote part of the territory of supply of the major cerebral arteries. However, the fact that all the seizures were focal and always of a similar focal pattern suggests a non-shifting origin for focal discharges, as would be expected with a fixed lesion. The cause of death was recent thrombosis of the anterior cerebral arteries, with massive infarction of both cerebral hemispheres—apparently precipitated by the pneumoencephalography.

Case IV.—M.G.H. 256154.

A 47-year-old woman with chronic rheumatic valvulitis and auricular fibrillation suffered an apoplectic incident manifested by a mild left hemiparesis from which she made a complete clinical recovery. Subsequently she developed recurrent left-sided and generalized seizures which began about a year after the "stroke." Death occurred more than six years later during a generalized seizure. At post-mortem examination the only lesion in the cerebral hemispheres was a large, old infarct in the right fronto-temporal region.

The patient, a 47-year-old white woman, was admitted to the Medical Service of the Massachusetts General Hospital on June 22, 1945, because of a "shock" of six hours' duration.

For many years the patient was known to have had rheumatic heart disease with mitral stenosis, mitral insufficiency, and aortic insufficiency, and there had been two previous admissions for acute rheumatic fever in 1940 and 1941. There was no history of auricular fibrillation.

About six hours before admission the patient suddenly developed weakness of the left side and was referred to the hospital by her local physician. She had had no previous neurological symptoms.

On physical examination, she was acutely ill, pale, and perspiring profusely. The temperature was 100° F., the pulse very rapid and irregular, the blood pressure 110 systolic, 80 diastolic. The lungs were clear. The heart was enlarged to the right and left; there was auricular fibrillation at a rapid rate; apical systolic and diastolic murmurs were heard. On neurological examination she was mentally clear, and had marked left facial weakness, deviation of the tongue to the left, flaccid paralysis of the left arm and slight weakness of the left leg. The tendon reflexes were depressed on the left side but the plantar reflex was flexor. Sensation was not tested. A lumbar puncture revealed no cells; the total protein was 23 mg. per cent. Serological tests for syphilis were negative. A chest X-ray confirmed the enlargement of the heart, especially in the region of the left auricle.

There was rapid improvement, and the patient was discharged eight days after

admission. At this time she was said to walk without difficulty. There had been considerable improvement in the motility of the left arm, but the left facial weakness was still prominent.

On May 29, 1946, the patient had her first seizure. In this, she recalled her head turning to the right, followed by a feeling of tingling in both arms and legs. She then lost consciousness for fifteen to thirty minutes, during which there were clonic movements of all four limbs. Following recovery of consciousness the left side was paralysed for about an hour. On examination the next day there was slight left lower facial weakness and deviation of the tongue to the left, but no demonstrable weakness of the limbs, though movements of the left arm and leg were awkward. The left knee-jerk was more active than the right but the plantar reflexes were flexor. All forms of sensation were intact. On lumbar puncture, the cerebrospinal fluid was under a pressure equivalent to 115 mm. of water and contained a total protein of 36 mg. per cent. An electroencephalogram on June 18, 1946, was characterized by diffuse bilateral 7–8 per second activity.

On December 18, 1946, she had signs of embolism to the right brachial artery, from which she made a spontaneous recovery.

On February 10, 1947, three days after discharge from hospital following a therapeutic abortion, the patient had a seizure which began with a "tightening in the face," followed by shaking of the arms, and then loss of consciousness. There was no residual weakness.

On March 7, 1947, she had a short seizure consisting of a momentary shaking of the left arm followed by a prickling sensation in the arm. On examination three days later no motor, reflex or sensory abnormality was found except for slight clumsiness of the left arm. Following this she took diphenylhydantoin 0·1 gramme, three times a day.

During the next four years there were no further seizures; the diphenlyhydantoin was discontinued in April 1949.

The patient meanwhile had increasing indications of congestive failure, and there was further evidence of peripheral arterial embolism; an embolus was removed from the left superficial femoral artery on February 5, 1951. On October 17, 1951, the patient developed symptoms and signs of an upper brain-stem infarction from which she recovered quite completely except for some residual weakness of the left leg.

The final admission on September 3, 1952, was occasioned by severe chest pain and increasing dyspnœa and orthopnœa. Shortly after admission the patient had a generalized convulsion and died.

Pathological Findings (*M.G.H. Autopsy No.* 15,725).

General: Autopsy was performed twelve hours after death. There was bilateral hydrothorax. The lungs were generally congested and œdematous; an old fibrous scar, representing an old infarct, was found in the left upper lobe. A white, well-organized adherent thrombus, thought to represent an embolus, occluded the pulmonary artery supplying this region. The pericardial sac contained 300 c.c. of clear, yellow fluid. The heart weighed 540 grammes and the left ventricular wall measured 15 mm. The right auricle was dilated. There was advanced mitral stenosis with fusion of mitral cusps and thickening of chordæ tendineæ. The valve opening was reduced to a slit which measured $1{\cdot}5 \times {\cdot}4$ cm. There were minimal rheumatic changes, without significant deformity, of the aortic and tricuspid valves. A large, $6 \times 1 \times {\cdot}5$ cm. yellow-red thrombus was found firmly attached to the endocardial surface of the left auricular appendage. There was minimal atherosclerosis of the coronary arteries and aorta. The lower abdominal aorta was completely occluded by firmly adherent red-grey thrombus which extended from a point 2 cm. distal to

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the origin of the renal arteries into both common iliac arteries. There were numerous depressed yellow-white scars of old infarction in the spleen and kidneys.

Neuropathological findings: The brain weighed 1,250 grammes. The major arteries at the base of the brain were patent and only minimally atherosclerotic. External examination disclosed a large depressed lesion (about 4 × 4 cm. in diameter by 3 cm. in depth) involving the anterior part of the right superior and middle temporal gyri, and posterior parts of the right middle and inferior frontal gyri extending to the central sulcus. Multiple horizontal sections after fixation in 10 per cent formalin, disclosed sharply outlined destruction of cortex and underlying white matter in the involved areas (fig. 4, A, B). The lesion extended deep into the hemisphere to include the anterior part of the insula, the external capsule, claustrum, lateral-anterior part of the putamen, genu and anterior limb of the internal capsule, and head of the caudate nucleus. No occluded vessels were found. Multiple microscopic sections from the edge of the lesion revealed findings consistent with an old infarct in which cellular activity had become quiescent (fig. 5B). Within the central part of the lesion, there were many interlacing strands of collagenous tissue, a few fibroblasts, and enmeshed within this area were a few pigment-filled macrophages. In the adjacent cerebral tissue there was a moderate increase in astrocytes, and, to a lesser extent, microglia. In a section which included the sensorimotor strip, large portions of the motor cortex were destroyed. Except for secondary degeneration of the internal capsule on the right, no other lesions were noted on gross and microscopic examination of the cerebral hemispheres. The secondary degeneration of the pyramidal tract continued through the brain-stem. Multiple small old infarcts were found in the mid-brain and pons.

Comment.—The cerebral lesion undoubtedly represented an old hæmorrhagic infarct which resulted from embolic occlusion of a part of the right middle cerebral artery. There was a source for emboli in the form of an endocardial thrombus, and embolism had occurred in other organs. The argument for an embolic basis for the cerebral infarction is strengthened by the absence of significant cerebral arteriosclerosis. A vascular occlusion could not be found, but it could well have become recanalized—a not unusual occurrence with lesions of this age. The transient hemiparesis which occurred about seven years before death could adequately be explained by the cerebral infarct. There were no other lesions in the cerebral hemispheres. The character of the infrequent seizures correlates well with a discharging focus near the site of the infarct. The first convulsion was delayed by nearly a year and although there were only 4 seizures, death occurred during one of them and may well have been hastened by the attack. Except for epilepsy, residual neurological symptoms and signs had been minimal.

Case V.—M.G.H. 243575.

A 64-year-old man had 3 episodes of left-sided status epilepticus over a one-year period. Although he never had an episode recognized as a "stroke," the initial seizures were immediately preceded by severe, oppressive substernal pain, clinically thought to represent a myocardial infarct. Death was related to a carcinoma of the œsophagus five years later. Post-mortem examination disclosed a large, old infarct involving the right superior temporal gyrus.

The patient, a 64-year-old white man, was admitted for the first time to the Massachusetts General Hospital on April 11, 1940, with the following history. He was apparently well until two hours before admission, when he experienced a sudden feeling of crushing and pressure over the lower sternum, which persisted. One hour later, the patient had a "prickly feeling" of his left hand and arm, became unable to speak, then all four limbs stiffened out and he had a series of clonic movements limited to the left side. During this seizure, the head and eyes deviated to the left, and he was apnæic, cyanotic, and incontinent of urine. The seizure lasted about two minutes and was followed by a state of unresponsiveness, during which the seizures recurred in a similar manner at ten to fifteen minute intervals.

On admission to the hospital the patient was unresponsive, breathing stertorously, and convulsing in the manner described above. The pupils were pin-point, but dilated during a convulsion. The eyes were conjugately deviated to the left. The pulse was regular at 85 per minute, the blood pressure was 170 systolic, 80 diastolic. Examination of the heart, lungs and abdomen showed no abnormal findings. Tendon reflexes were sluggish but equal in the arms; in the legs the tendon reflexes were brisk, except for the left knee-jerk which could not be obtained. The plantar reflex was flexor on the right and absent on the left. No changes in muscular tone could be discerned.

Within several hours after admission, the blood pressure fell to 90 systolic, 60 diastolic, and then quickly and spontaneously rose to 130 systolic, 85 diastolic. At that time, consciousness began to return, and he was alternately agitated and drowsy. He complained of thirst, "crawling" sensations in his left hand, and "burning" in the left arm and left chest. On re-examination it was noted that there were no longer any ocular abnormalities, no facial weakness, and no loss of motor or sensory function; the tendon reflexes were present, brisk, and equal throughout, and the plantar reflex was flexor on both sides.

The white blood cell count on admission was 25,000. A lumbar puncture showed an initial cerebrospinal fluid pressure equivalent to 50 mm. of water; the fluid contained no cells. Electrocardiograms were taken on April 12, 13, 14, and 18; excepting for a flattened T_3 on one occasion and a low R_1 on another, there was no evidence of myocardial infarction. A chest roentgenogram showed only slight cardiac enlargement to the left. Skull roentgenograms were normal. An electroencephalogram showed intermittent generalized 6 per second and 7–8 per second activity. The lumbar puncture was repeated and found to be normal in all respects.

From the second hospital day the patient felt well. Except for a questionable left facial weakness, repeated neurological examinations disclosed no cranial nerve, motor, reflex, or sensory abnormalities. Similarly retinoscopic and visual field examinations were within normal limits. On April 25, 1940, the patient left the hospital against advice.

The patient was free of symptoms following discharge from the hospital until July 29, 1940. On that day he had a series of seizures, five in all; from the family's description they seemed to be left sided. On admission to the Boston City Hospital, he was confused and unco-operative, complaining only of pain along his entire left side. Examination disclosed less active reflexes on the left, and a transient extensor plantar reflex on the right. As before he left the hospital against advice as soon as he had fully regained consciousness.

The patient was then well until April 11, 1941, when he was readmitted to the Boston City Hospital following a series of six left-sided seizures. These seizures were preceded by a sense of oppression under the sternum, as well as a feeling of rotation. Following the last of this group of seizures he was unresponsive for almost a day. On physical examination, no abnormalities were found except for indistinctness of the disc margins and hyperactive but equal tendon reflexes. During the examination he had a few clonic jerks of the arms. Laboratory investigations,

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which included a blood test for syphilis and routine blood determinations, were normal.

The patient then remained well until the end of 1944, when he developed anorexia, anterior chest pain on eating, and inability to retain food for more than a few minutes. These symptoms progressed and resulted in a considerable loss of weight. He was finally admitted to the Boston City Hospital on September 20, 1945. On examination he was mentally clear, alert, well oriented and co-operative. Temperature, pulse, respiration and blood pressure were normal. As on previous examinations, the disc margins were indistinct, but there was no papilledema, and the cranial nerves were intact. There was marked general wasting, but strength was adequate considering the great loss of muscle bulk. Tendon reflexes were all present, brisk, and equal, and the plantar reflexes were flexor. Sensation was normal throughout. Examination of the urine, blood and spinal fluid revealed no abnormalities. Roentgenograms of the skull and chest were negative. Carcinoma of the œsophagus was demonstrated by roentgenologic and œsophagoscopic examinations. After the œsophagoscopy, he developed cervical emphysema and respiratory obstruction, and he died on October 7, 1945.

Pathological Findings (*Boston City Hospital Autopsy No.* A45–471).

General: Autopsy was performed several hours after death. There was an epidermoid carcinoma of the œsophagus with metastases to the liver, the left kidney, and the regional lymph nodes. In addition there was bronchopneumonia, and subcutaneous emphysema. The heart was normal in all respects.

Neuropathological findings: The brain was examined after fixation in 10 per cent formalin. As viewed from the external surface it was generally not remarkable. The large arteries had thin walls and were patent. Examination of coronal sections showed that the right superior temporal gyrus and adjacent white matter were incompletely destroyed and replaced by multilocular cavities (fig. 6). In several places the cerebral cortex was missing and the exposed white matter was brown in colour. The tissue adjacent to these cavities was firm in consistency and greyish-brown in colour. In size, this lesion was about 2·5 cm. in width, 0·5 cm. in vertical diameter and about 4–5 cm. in antero-posterior diameter. As a result of the loss of tissue the insula was unusually exposed and the space about it increased. The corticospinal tract was little affected, though at one point in the right internal capsule there was a greyish discoloration 3 mm. in diameter. There was no definite descending degeneration of the cortico-spinal tract. The lateral ventricles were about normal in size though the temporal horn of the right lateral ventricle was slightly dilated. No other gross lesions were seen.

Microscopically, the lesion was sharply demarcated from the surrounding normal brain tissue. In its periphery, there were many large astrocytes and a few macrophages containing blood pigment, but the cerebral cortex and white matter a very short distance away were within normal limits. The interior of the cavity was traversed by connective tissue and small blood vessels, with a very few pigment-laden macrophages in the interstices of this meshwork. The large and small blood vessels were normal. The appearance of the lesion was consistent with an old cerebral infarct within which cellular activity had become quiescent.

Comment.—In this case, the disorder of the nervous system was limited to three episodes of recurrent convulsive seizures, with no neurological abnormalities in the periods between seizures. Post-mortem study disclosed a single cerebral lesion, located in the right temporal lobe. The recurrent left-sided convulsions without residual neurological changes can

be adequately explained by the presence of a lesion so placed. The appearance of this lesion was typical of old cerebral infarction, in the region of supply of a branch of the right middle cerebral artery. The presence of blood pigment within the lesion suggests that it was originally hæmorrhagic. No vascular occlusion was found, but the absence of any significant degree of arteriosclerosis or other vascular disease, and the hæmorrhagic nature of the infarct, suggest that it may have been the result of a cerebral embolus, even though post-mortem examination did not reveal a source for emboli.

Case VI.—Boston Veterans Administration Hospital 368.

A 50-year-old woman with chronic rheumatic valvulitis and auricular fibrillation suddenly developed dysphasia and right hemiparesis two and a quarter years before death. She recovered only partially from this and a year later had her first generalized seizure. Two weeks before death she was in status epilepticus for a three-day period, the seizures being characterized at their onset by a deviation of the eyes to the right. The immediate cause of death was infarction of the small bowel, a consequence of an embolus to the superior mesenteric artery. The only cerebral lesion at post-mortem examination was a large, old infarct in the left fronto-temporo-parietal region.

The patient, a 50-year-old nurse, was apparently in good health until late March 1950. At that time, she began to suffer from paroxysmal nocturnal dyspnœa, orthopnœa and dependent œdema. She was treated with digoxin, and was doing well until April 26, 1950; on that day she suddenly developed right hemiplegia and aphasia and was admitted to Boston City Hospital. Pertinent findings on this admission included right hemiplegia, receptive and expressive aphasia, enlargement of the heart with grossly irregular rhythm, a soft rumbling apical diastolic murmur and an accentuated mitral first sound. She was given digitalis, and physiotherapy was begun. On May 17, 1950, she was transferred to the Cushing Veterans Administration Hospital. At that time she was able to speak only a few simple phrases, but could comply with spoken requests. The temperature was normal, the heart-rate was 72 and grossly irregular, the blood pressure 124 systolic, 70 diastolic. There was a right lower facial weakness; no movement was noted in the right arm, and in the leg only slight flexion and adduction at the hip were possible. No increase in tone was detectable in the right limbs, although the tendon reflexes were hyperactive and the plantar reflex extensor on that side. There was a slight blunting to painful stimuli on the entire right side, but no other sensory defect.

Laboratory studies included normal hæmoglobin, hæmatocrit and white blood cell values; the serological tests for syphilis were negative; the urine at times was clear, at other times it contained many white and red cells. The sedimentation rate was 39 mm. per hour. Rehabilitation training was continued throughout her hospital stay, with improvement in both speech and motor function. Several weeks after admission conversion of the auricular fibrillation to regular sinus rhythm was effected by the use of quinidine. When the cardiac rhythm became regular, a presystolic mitral murmur was heard, and there was electrocardiographic evidence of auricular enlargement. Roentgenograms of the chest revealed enlargement of the left atrium and auricular appendage, the right ventricle and the pulmonary conus.

On March 16, 1951, while on the way to physiotherapy, the patient turned round in the hallway, stiffened, and fell to the floor. She made chewing movements, had coarse jerky movements of the limbs, and became cyanotic. When first seen by a physician, she was lying on the floor, flaccid and unresponsive, with some frothing

at the mouth, and breathing heavily. The cardiac rhythm was regular at 110 per minute, and the blood pressure was 145 systolic, 90 diastolic. Her lower lip was lacerated. She quickly regained consciousness, whereupon the neurological examination was the same as before the seizure. She was given phenobarbital 30 mg. four times daily, and remained free of seizures until discharge on May 1, 1951.

On July 7, 1952, the patient was readmitted to the Cushing Veterans Administration Hospital. In the preceding fourteen months she had done well at home, taking phenobarbital and quinidine as prescribed. Four hours prior to this admission, she had a sharp knife-like pain in the right lower quadrant of the abdomen. There were no associated gastro-intestinal or urinary symptoms. The pain was said to radiate into the right inguinal region, and had persisted from the time of onset until admission. Examination was very much the same as when she left the hospital; cardiac rhythm was regular at 88 per minute, and the neurological signs were unchanged; there was tenderness and muscular resistance over the right side of the abdomen. Laboratory studies were essentially normal, except that the electrocardiogram revealed auricular flutter. Digitalis was given. After a ten-hour observation period an exploratory laparotomy was done but examination of the peritoneal cavity revealed no cause for the abdominal symptoms. She did well post-operatively until the second day, when she developed gross hæmaturia which persisted for forty-eight hours. The cardiac rhythm kept changing from auricular flutter to fibrillation, and could not be corrected with quinidine. Phenobarbital had been discontinued since the time of admission.

On July 14, 1952, she began to have seizures, and in the next three days had 6 to 10 daily. They were generalized clonic convulsions which began with deviation of the eyes to the right, immediately followed by loss of consciousness, cyanosis, and frothing at the mouth. Except for slight confusion lasting for several minutes after each seizure, there was no change in the neurological findings from the previous examinations. During this period heavy sedation with barbiturates was given, and her state of consciousness varied from drowsiness to coma. A lumbar puncture was performed, with unsatisfactory results. She then remained in a drowsy state, despite reduction in sedation, and became incontinent of urine and fæces. She had been afebrile the first week, but afterwards ran a daily fever of 101–102° F., despite treatment with penicillin and streptomycin. In the last week of her illness, she developed cyanosis, dyspnœa, distension of neck veins, râles at the right lung base and her respirations became more rapid. There was no response to oxygen therapy or increases in digitoxin dosage. On July 27, 1952, the right leg and thigh became œdematous, cold and cyanotic, and she developed the symptoms and signs of bowel infarction. The patient became progressively worse and death occurred on July 31, 1952.

Pathological Findings. (*Boston V. A. H. Autopsy No.* A52-10).

General: Autopsy was performed eight hours after death. The heart weighed 390 grammes. In the left auricle there was a thrombus, firmly adherent to the wall. The mitral valve was thick and calcified, and failed to admit one finger. The tricuspid valve also was thickened, the cusps fused, and the orifice narrowed. There was a saddle embolus at the bifurcation of the abdominal aorta extending into the left and right iliac arteries. A branch of the superior mesenteric artery, and the right renal artery, were also occluded by emboli. A portion of the small bowel about 30 cm. proximal to the ileocæcal valve was gangrenous. There were old areas of infarction in the left kidney, and a fresh large, recent anæmic infarct in the right kidney.

Neuropathological findings: The brain weighed 1,175 grammes. The external appearance was not remarkable except for an extensive lesion in the left hemisphere

(fig. 7A). Here there was destruction of the cerebral cortex and depression of the surface of the brain in an area measuring about 10 cm. in length by 2 cm. in width. This lesion involved the cortex bordering the Sylvian fissure, and included the superior temporal and a portion of the middle temporal gyri, the insula, and the inferior parietal lobule (including the supramarginal gyrus) as far posteriorly as the parieto-occipital junction. After fixation in 10 per cent formalin the brain was cut in horizontal sections; the lesion was seen to extend medially into the cortex and white matter of the opercular portion of the inferior frontal gyrus (fig. 7B). The cut surface of the lesion showed it to be a large cavity lined externally by the pia-arachnoid, and traversed in the centre by delicate web-like material (fig. 8). Microscopically, the cavity contained a network of vessels and collagenous fibres, in the spaces of which there were innumerable macrophages. Many of these phagocytes were filled with granules of blood pigment. In the cerebral tissue surrounding the cavity, there were large numbers of plump astrocytes and extensive fibrous gliosis (fig. 8). Nerve cells and fibres immediately surrounding the lesion had disappeared. Several small arteries were included in the sections; these were normal in appearance.

Comment.—The hemiplegia and aphasia which developed suddenly two and a quarter years before death are well explained by the only cerebral lesion, a large old infarct in the left fronto-temporo-parietal region. No occluded cerebral vessels were found at autopsy, but the finding of a mural thrombus in the left auricle, the repeated episodes of auricular fibrillation and the evidence of recent and old embolic occlusion of major arteries elsewhere in the body, with infarction of kidneys and bowel, all strongly favour an embolic basis for the cerebral infarction.

The convulsive seizure which occurred a year after the apoplectic episode and the repeated seizures two weeks before death can reasonably be related to the cerebral lesion found on post-mortem examination. Although the seizures were described as generalized, the constant deviation of the eyes to the right during the convulsive attacks suggests a focal onset referable to the left side of the brain. It is of interest to note that in this case, the cerebral lesion resulted in severe residual neurological symptoms and signs in addition to the seizures, in contrast to the relative lack of such findings in the previous cases.

Discussion

The clinical and pathological data from our case material are summarized in Table I.

The pertinent literature emphasizing the relationship between vascular disease of the brain and epilepsy has been reviewed. For the most part, the papers on this subject have discussed the problem in general terms, with very few case reports containing adequate clinical and pathological data. It is therefore difficult to compare the findings in our cases with those of most other authors. The available reports of cases of vascular disease with recurrent convulsions are summarized in Table II.

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Clinical Aspects

(*a*) *The "stroke"—its development and course.*—There was great variability in the severity of initial neurological symptoms and signs. In Case 1, for example, there was no discrete episode of apoplectiform character that could be identified with certainty; instead, the illness began with a focal sensory seizure. Objective signs of neurological abnormality, aside from seizures, were notably absent. In Case 3, neurological symptoms and signs gradually accumulated over a six-month period, and were clearly preceded by Jacksonian seizures. In Case 5, the illness began abruptly with a flurry of left-sided seizures, followed by a transitory depression of tendon reflexes on that side; no additional neurological findings appeared, although focal seizures occurred at intervals for the next year. In contrast to these cases, focal neurological signs of sudden development marked the onset of the illness in the remaining 3. In 2 of these, they were of an evanescent nature: in Case 2, there was a facio-brachial monoplegia with aphasia which subsided completely within three to four weeks; in Case 4, the patient had a left hemiparesis which appeared abruptly, but signs of this were no longer detectable after a few weeks. Only in Case 6 did the initial neurological disability associated with the "stroke" persist throughout the course of the illness.

Cases previously recorded in the medical literature have shown this same variability in the clinical manifestations of the initial apoplectic attack. The majority of published cases have resembled our Case 6 in which neurological symptoms were observed at the time of the "stroke" and, despite some improvement, persisted until death. Jackson (1931, p. 458) cited the case of a physician who suffered from focal epilepsy which was the only sign during life of a small infarct of the left uncinate gyrus, and, in the case of Williamson and Simson (1934), an initial hemiparesis subsided before the advent of seizures. Gowers (1901) and Jackson (1931) have emphasized the fact that the indications of an apoplectic event may be absent in patients who subsequently develop epilepsy on the basis of a focal vascular lesion, or that recovery from a "stroke" may take place before the development of recurrent seizures.

(*b*) *The epileptic manifestations.*—The interval between the "stroke" and the beginning of seizures varied widely. As already noted, seizures marked the onset of the neurological illness in 3 of our cases (1, 3 and 5). In Case 2, there was an interval of ten days between the development of focal signs and the first convulsive attack. The longest interval was eleven months, in Cases 4 and 6. These findings are in agreement with those reported in the literature. Gowers (1893) commented that when seizures follow hemiplegia in adult life, they usually commence within "a few

months, or at most a year." He further stated that "chronic recurrent fits date from the onset in about one-third of the cases." Krapf (1932) and Fisher (1951) have each reported a single case in which the interval was two years. These instances are exceptional, however; most other authors have recorded relatively short latent periods, and have confirmed the high incidence of seizures at the time of the original apoplectic episode.

It is noteworthy that in all of our cases, the seizures had focal aspects. Thus, in Case 1, there were at least 2 episodes of paræsthesia in the left arm; in Case 2, there were chewing movements followed by clonic jerking of the face and right arm; in Cases 4 and 6 seizures began with turning movements of the head and eyes to the right, and in Case 4 there was jerking of the right arm on one occasion; in Case 5, the seizures were always confined to the left side. Only in Case 3 was there a recurrent seizure pattern characteristic of a Jacksonian march. In 4 cases (1, 2, 4 and 6), there were generalized seizures as well. These usually had a focal onset, but occasionally were generalized from the beginning. The seizures were focal, or had focal aspects, in 12 of the 21 previously reported cases; generalized seizures alone were described, or implied, in the remainder.

There was considerable disparity in the frequency of seizures. In 2 cases (5 and 6), the seizures tended to occur in groups or in bursts. In Case 5, a flurry of seizures occurred three times during the first year, and then the patient was free of attacks until his death five and a half years after the "stroke"; in Case 6, after an isolated seizure in the first year of the neurological illness, there was a bout of 30 attacks in the following year. As shown by these cases, there was great variability in the frequency of the seizures in any one case. This characteristic is further exemplified by Case 3, in which over a six-month period, seizures gradually increased in frequency from one or two a month at first to as many as one or two a day in the last three months. In Case 4, there were 2 seizures during the first year after the "stroke," 1 during the second year, an interval of freedom for five years, and, finally, death during a convulsion. In general, the attacks were not frequent (Table I), and in this respect our cases resembled those reported by Gowers (1893, 1901) and others.

The duration of the epilepsy, like the other clinical features, was extremely variable. Thus one of the patients (Case 4) survived for seven years after the onset of epilepsy, while another (Case 3) survived for only six months. In Case 5, the patient remained free of seizures after the first year until death from unrelated illness over four years later. We have arbitrarily excluded from this report instances of seizures of very short duration, in which death occurred during the acute phase of the cerebral lesion. It is impossible to predict how many of these patients would have

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developed epilepsy had they survived. Also, some patients with serious associated illnesses died from causes unrelated to the epilepsy; it would be equally difficult in these cases to decide how long the seizures might have continued.

There can be no doubt that the epilepsy may be of very long duration. Lehard (1912) reported the case of a patient with a small, old frontal infarct who had suffered for thirty years from recurrent seizures. Anglade and Jacquin (1908) described a case of similar duration, and Bruetsch (1942) reported 2 cases with seizures for twenty-six to twenty-seven years. It should not be inferred, however, from the foregoing remarks that post-apoplectic epilepsy is always a benign condition, for in our Cases 1 and 4 death could be directly attributed to convulsive seizures. Similarly, in the cases reported in the literature by Jentzer and de Morsier (1932) and Mouisset, Nové-Josserant and Bouchut (1911) and in 2 of those studied by Fisher and Adams (1953) death occurred during a convulsion.

(*c*) *Electroencephalographic findings.*—Electroencephalograms were available for study in all but Case 6. In general, the abnormalities in these records tended to be diffuse or poorly localized, and no instances were discovered of focal or paroxysmal seizure discharges, although activating procedures were not employed. Where there was a difference in the degree of abnormality between the 2 sides of the head, as on the initial examination in Case 2, and in both records in Case 3, the greater abnormality was on the side of the lesion. In each of the other cases, only one electroencephalogram was done. In Cases 4 and 5 these were performed during intervals between seizures and showed little if any abnormality. In Case 1, examined during the post-ictal confusional state, there was severe generalized abnormality. Complete electroencephalographic studies were not carried out in any of our cases, so that on the basis of our material, a true appraisal of the value of this laboratory method cannot be made. No reference to electroencephalograms was made in any of the pathologically proven cases in the literature.

Pathological Aspects

(*a*) *The nature of the cerebral lesions.*—In all of our cases, recurring seizures were consequent to cerebral infarction. Furthermore, in a study of 104 consecutive cases of cerebral infarction and hæmorrhage (Richardson and Dodge, 1954), only one example of recurring seizures resulting from cerebral hæmorrhage was encountered, whereas there were 5 cases of recurring seizures following infarction. Jackson (1931) and Gowers (1901) were of the opinion that epilepsy was more commonly seen with cerebral infarction than with hæmorrhage but, as already stated, they

had no pathological confirmation of this impression. In our survey of the literature the case of Williamson and Simson (1934) provided an example of epilepsy following cerebral hæmorrhage, and in 2 of 59 cases of hypertensive encephalopathy studied by Fisher and Adams (1953) recurring seizures were apparently the result of small superficial cerebral hæmorrhages. The reasons why epilepsy is more commonly encountered after cerebral infarction than after hæmorrhage are quite evident. Firstly, hæmorrhage is in most cases fatal; secondly, the cortex is more frequently involved with infarction; and finally, cerebral hæmorrhage is only about one-fifth as common as cerebral infarction (Adams and Vander Eecken, 1953; Richardson and Dodge, 1954). Aring and Merritt (1953) make the statement that seizures more frequently complicate hæmorrhage than infarction, but refer only to the acute episode; their paper gives no data concerning the incidence of recurring seizures following vascular lesions, and it is not clear from their account that a distinction was made between hæmorrhage and hæmorrhagic infarction.

In our cases, the cerebral lesion considered to be related to the seizures was typical of old infarction and involved the cerebral cortex. The changes in the cortex adjacent to the lesion were in no way different from those observed in cases of cerebral infarction of similar age in which no seizures have occurred. In Cases 2, 4, 5 and 6, the presence in the lesions of macrophages containing blood pigment suggests that the infarction was originally hæmorrhagic.

The size of the lesions varied considerably. In Cases 1 and 3 they were small, measuring from a few millimetres up to 2 cm. in diameter. Larger foci, several centimetres in extent, were found in the other cases. This suggests that size alone is not an important factor in determining the epileptogenic potentialities of the lesions. It should be emphasized that the lesions involved the cerebral cortex in all cases, and that they were located in, or in the vicinity of, the sensorimotor areas. In Cases 1, 4, 5 and 6, the infarcts in the cerebral hemispheres were solitary, whereas in Cases 2 and 3 multiple cortical infarcts were found. Solitary lesions were found in about half of the cases previously reported by others. Of the 21 cases reported in the literature, there were grossly visible lesions of the cerebral cortex in 18. In the other 3 cases, the lesions were situated in the subcortical white matter immediately beneath the cortex; in these the pathological studies were not sufficiently complete to exclude the possibility of microscopic changes in the cortex. As in our cases, the lesions reported in the literature varied considerably in size. They were rather widely distributed throughout the cerebral hemispheres; but often were found in the central and Sylvian regions.

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(*b*) *Pathogenesis of cerebral lesions.*—In Case 3, the multiple small old infarcts in the left cerebral hemisphere can be related to the presence of thrombosis of the left internal carotid artery. Presumably, the thrombosis occurred on the basis of severe atherosclerosis. Examination of the cerebral vessels in the remaining 5 cases disclosed no evidence of vascular occlusion. The carotid and vertebral arteries in Cases 1, 2 and 4 were injected in the neck with water at autopsy and found to be patent. Although it is impossible to be certain as to the cause of the infarction in these 5 cases, there is presumptive evidence that it was the result of embolic vascular occlusion. Thus, in Cases 2, 4 and 6 there was a demonstrable source of emboli in the heart, and there were multiple infarcts in other organs where thrombotic occlusion of vessels is rare. Rheumatic heart disease with mitral stenosis, auricular fibrillation, and mural thrombus formation within the left auricular appendage was the background for embolic phenomena in Cases 4 and 6, and in Case 2, there was a mural thrombus on the endocardial surface of the left ventricle as a consequence of myocardial infarction. No source of emboli was found in Cases 1 and 5, but the patient in the former case had had auricular fibrillation during life, and in the latter the first seizure was preceded by an episode which suggested myocardial infarction. Furthermore, as previously noted there was microscopic evidence to suggest that the infarction was originally hæmorrhagic in Cases 2, 4, 5 and 6; and hæmorrhagic infarction, as pointed out by Fisher and Adams (1953) and Kubik (1953), is most commonly the result of embolism—an observation which is in agreement with our experience. Moreover, the studies of Fisher (1953) suggest that small infarcts of the cerebral cortex are nearly always embolic. There was severe atherosclerosis, of a degree that could lead to thrombosis, in the cerebral arteries in Cases 2 and 3; in the others, atherosclerosis was minimal or absent, and there was no evidence of other disease of the vessel walls.

From the data presented in the previously reported cases of cerebral infarction followed by epilepsy, it is even more difficult to determine the pathogenesis of the cerebral lesions. Thrombotic occlusion of cerebral arteries was described in only 3 cases (de Morsier and Fischer, 1934; Marinesco and Kreindler, 1936; Fisher, 1951). Bruetsch (1942) found, in association with the cerebral lesions, "fibrous tissue plugs" in small vessels, which he interpreted as "rheumatic endarteritis." An alternative explanation for these vascular changes, and one which we favour, is that they represent the end stages of embolic vascular occlusion. Our experience with other pathologically examined cases favours this view; moreover, Harrison (1948) and Barnard (1953) have demonstrated ex-

perimentally that emboli, after sufficient time has elapsed, may present an appearance similar to that described in the cerebral vessels by Bruetsch. Rheumatic valvulitis was an associated finding in the cases reported by Naunyn (1895), Lehard (1912), and Bruetsch (1942), and the findings in the heart in the 2 cases reported by Anglade and Jacquin (1908) are best explained on the basis of rheumatic heart disease. An embolic basis for the cerebral lesions in their cases is therefore strongly to be suspected. In the remaining cases the cerebral lesions described are typical of infarction, but their pathogenesis remains obscure.

Correlations and Speculations

The problem created by epilepsy beginning in adult life is one which has occupied the attentions of many physicians in the past and still represents a formidable problem. The possible causes of this symptom have been discussed under various headings including "late epilepsy," "épilepsie tardive," "Spätepilepsie" (Marchand and Nouet, 1907, Savill, 1909; Redlich, 1927; Riesman and Fitz-Hugh, 1927; Krapf, 1932; von Hoesslin 1935), "senile epilepsy" (Sympson, 1894; Naunyn, 1895; Allen, 1897–1898, "arteriosclerotic epilepsy" (Gordon, 1935, 1951; Tompkins, 1939), "rheumatic epilepsy" (Bruetsch, 1942), "cardiac epilepsy" (Chadbourne, 1903; Lehard, 1912) and "post-hemiplegic epilepsy" (Gowers, 1901; Dunham, 1916). Unfortunately, the clinical data in many of these reports are incomplete, and pathological confirmation of the clinical impressions often was not obtained. We are unaware of a single series of unselected cases of late life epilepsy in which the clinical diagnoses have been adequately confirmed by pathological study. Without such study, any statement as to the relative incidence of pathological conditions producing seizures in adulthood lacks authority. Not only may the primary clinical diagnosis be in error, but there may be more than one potentially epileptogenic disease process in the brain. For example, in a recent study of the incidence of seizures resulting from cerebral vascular disease (Richardson and Dodge, 1954) it was necessary to exclude several cases because of the co-existence of cerebral infarction or hæmorrhage with tumour, encephalitis, or traumatic scars. Nevertheless, it has been the general impression of most observers that cerebral vascular disease is of great significance in the production of epilepsy. The clinical study of Walker (1936), and the clinical impressions of Robertson (1937), Penfield and Erickson (1941), and of Lennox (1953) suggest that after the fifth or sixth decade, vascular disease is one of the most important factors underlying the epileptic state. Yet the answer to the question as to the relative frequency of this and various other diseases in the causation of epilepsy in adult life

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must still await an answer by definitive clinical and pathological studies.

It is well to mention at this point that on the basis of our experience, it is the *cerebral lesion* brought about by the vascular disease, and not the vascular disease of itself, that is of greatest significance in the production of recurring convulsive seizures. We have found that epilepsy is about five times as frequent in patients with vascular lesions of the brain parenchyma as it is in those with cerebral atherosclerosis alone (Dodge and Richardson, 1953). It must be admitted, however, that convulsive seizures without grossly demonstrable structural change in the brain may occur with acute cerebral ischæmia from any cause. Stokes-Adams attacks (Stokes, 1846; Benham, 1887; Bristowe, 1894) are an excellent example, and the convulsive seizures resulting from compression of the carotid arteries, first noted in man in 1859 by Kussmaul and Tenner, provide another. The seizures which sometimes attend the onset of cerebral embolism or, less often, thrombosis may likewise be explained on the basis of ischæmia (Richardson and Dodge, 1954). Certainly, convulsions may occur prior to the development of other neurological signs, and the presumption is strong that they may precede any significant structural change within the brain. It is our belief, therefore, that the "acute" seizures occurring in the initial stages of cerebral vascular lesions should be considered separately from the epilepsy resulting from an old vascular lesion.

The universal involvement of the cerebral cortex (or, in rare instances, the immediately adjacent subcortical white matter) has been stressed. The selective character of the neurological signs, their transient nature, and the seizures themselves seem readily explicable by the cortical location of the pathological changes. But, what is there about these cortical scars that renders them epileptogenic? This is a question which has excited the interest of many investigators for several generations. In recent years, Penfield and his associates, in particular, have devoted themselves to the study of this problem. Much significance has been attached to the transition zone between the normal cortex and the scar, where a variety of neuronal, glial, and vascular aberrations have been observed (Penfield and Humphreys, 1940). We have seen similar changes in our case material, but have found them difficult of interpretation, for they appear to be no different in degree or kind from those occurring in lesions unassociated with epilepsy. The ingenious theory of Penfield based on the supposed critical nature of the blood supply at the edge of a cortical scar, though attractive, is not firmly established in fact. These authors have also drawn attention to meningo-cerebral scarring as a cause of epilepsy. This type of lesion, which is usually traumatic and does not occur as a result of vascular disease, cannot be responsible for seizures resulting from cerebral

infarction or hæmorrhage. It is obvious that the mechanism of seizure discharge cannot be fully elucidated by pathological methods alone, and electrophysiological methods likewise can merely reflect the presence of an abnormal neuronal discharge, but not explain it. The demonstration by Forster (1945) of the convulsant properties of acetylcholine has stimulated interest in its possible importance in spontaneous seizure production. In 1947, Pope and his co-workers found a small but significant increase in cholinesterase activity in "epileptogenic areas" of monkey and human cortex. Recently, Tower (1952) has presented further data which suggests that there is a defect in acetylcholine metabolism in "epileptogenic foci," and that hypoxia increases this abnormality. Provocative as these studies are, their significance must wait further investigation.

A question frequently asked is why patients with cerebral infarction or hæmorrhage are less likely to develop epilepsy than those with traumatic cerebral scarring. We believe that the answer to this question lies in the fact that the cerebral cortex is often not affected in vascular lesions, while it is almost universally damaged in cerebral injury resulting from trauma. (Richardson and Dodge, 1954) found the incidence of epilepsy as a sequel to cerebral infarction to be 26 per cent (6 of 22 cases) when only those cases with chronic lesions of the cortex were considered. This is close to the incidence reported by Wagstaffe (1928), 18·7 per cent, Ascroft (1941), 34 per cent, Russell and Whitty (1952), 43 per cent, and Watson (1952), 41·6 per cent following penetrating head injury. A strict comparison of our case material with the data on traumatic brain injury is not possible because of the relatively small number of cases on which our figures are based. Nevertheless, it is probable that our figures are artificially low, for the clinical data were obtained from the hospital records and not by direct interrogation of the patient and family—a method of study employed by Russell and Watson. We believe that these findings underlie a fundamental concept which bears re-emphasis—*that it is the cortical site, rather than the nature, of the destructive cerebral lesion that determines its epileptogenic properties.*

Mention should be made of another form of cerebral vascular disease commonly associated with convulsive seizures—namely, hypertensive encephalopathy. This condition presents a complex problem, which is currently under investigation by Adams and Fisher (cf. Adams and Vander Eecken, 1953). A preliminary survey of their data has shown that convulsive seizures occurred in about one-third of their 59 cases. In 4, the seizures were recurrent, and in all of these, lesions of the cerebral cortex were found.

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Practical Considerations

When confronted with the problem of epilepsy developing in adult life, how may one logically reach the conclusion that the epilepsy is on the basis of a vascular lesion, rather than other disease? If neurological symptoms and signs have developed suddenly, with or without initial convulsions, and then, after a period of recovery, recurrent seizures supervene, the diagnosis should be seriously considered. This is especially true if the seizures are focal and involve the parts of the body originally affected. The impression is strengthened when the neurological symptoms develop on a background of cardiovascular disease, such as myocardial infarction, rheumatic heart disease, auricular fibrillation, hypertension, or generalized arteriosclerosis. Under these circumstances, a programme of conservative management with anticonvulsant medical therapy would seem justified while extensive and hazardous diagnostic procedures seem unwarranted.

When recurring seizures develop without evident pre-existing neurological disease, among the conditions to be considered are Stokes-Adams attacks. The history is such cases may give evidence of irregularities of cardiac rhythm, and the convulsions are usually preceded by faintness or syncope. Further examination, including electrocardiography, will establish this diagnosis. In some other cases, the development of seizures without preceding events such as "stroke," head trauma, syphilis, intoxication or a progressive course may well be the result of a small cortical infarct, although clear evidence of the presence of such a lesion may not otherwise be demonstrable. Further difficulty in diagnosis is provided by a group of patients with occlusive cerebral vascular disease, especially of the internal carotid, vertebral, and basilar arteries. These patients may have transitory stereotyped attacks of neurological deficit, often difficult to distinguish from seizures. Although the exact explanation of this phenomenon is not known, the clinical features of the syndrome have been well described by several authors (Frøvig, 1946; Llavero, 1948; Fisher, 1951; Denny-Brown, 1951). In all these instances, the plan of action should be conservative, although the patient should be kept under close medical supervision.

The greatest difficulty arises when the neurological symptoms and signs and the seizures themselves seem to be progressively increasing in severity. Under such circumstances, an expanding intracranial lesion must be suspected, and further procedures required to establish this diagnosis must be given serious consideration. If the progression has been step-like rather than of gradual development, the case for cerebral vascular occlusion, particularly of the internal carotid artery, is strengthened. It is of practical importance to make such a distinction clinically, if possible, in order to

avoid procedures such as pneumoencephalography and angiography which are not without danger to the patient. The hazard in such cases is exemplified in our Case 3, in which massive bilateral cerebral infarction and death immediately followed a pneumoencephalogram. Similar accidents following pneumoencephalography in patients with carotid artery occlusion have been reported by Fisher (1951) and Denny-Brown (1951). Various neurological complications, including transitory or permanent hemiplegia, may occur following carotid angiography (Dunsmore, Scoville and Whitcomb, 1951; Abbott, Gay and Goodall, 1952). However, so common is the clinical teaching today that cerebral infarction rarely, if ever, produces epilepsy, that when a patient in adult life develops recurring convulsive seizures, special diagnostic procedures are often undertaken without adequate preliminary investigation and consideration.

Summary and Conclusions

Cerebral infarction is an important and often overlooked cause of recurrent convulsive seizures in adult life. Six cases are presented with clinical and pathological findings, and are compared with additional cases from the literature.

In all of our cases the infarction involved the cortex of the central or Sylvian regions. The lesions were quiescent or resolving, and varied in size from a few millimetres to several centimetres in diameter. There was evidence in 5 cases that the infarcts were embolic. In 1 case, there was thrombosis of an internal cartoid artery.

The seizures in each case had focal aspects, but were associated with generalized convulsions in 4. Seizures appeared in 4 cases within a period of time varying from ten days to eleven months after the apoplectic attack. In 1 case, evidence of cerebral disease, except for the seizures, was totally lacking. In 1 instance seizures preceded the development of neurological signs, and the illness pursued a progressive course. The focal neurological signs in 3 of the other 4 cases were transient and subsided completely, leaving epilepsy as the only symptom, and in the remaining case there was incomplete recovery from hemiparesis.

The frequency of attacks and duration of the convulsive state were extremely variable. In 1 case the seizures ceased after one year, and had not recurred to the time of death four and a half years later. In the remaining cases the seizures continued at irregular intervals for the rest of the patient's life. Death could be directly attributed to a convulsive seizure in 2; 3 patients died from causes unrelated to the neurological disease. One patient, with thrombosis of the internal carotid artery, died with extensive

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fresh thrombosis of the anterior cerebral arteries and massive cerebral infarction after a pneumoencephalogram.

The importance of involvement of the cerebral cortex in the pathogenesis of the seizures is emphasized. It is suggested that the incidence of epilepsy following infarction of the cerebral cortex may approach that following traumatic cerebral injury.

The clinical problem of differential diagnosis is discussed. The dangers of hazardous diagnostic procedures such as pneumoencephalography in patients with cerebral vascular disease are re-emphasized.

ACKNOWLEDGMENTS

We wish to express our thanks to Dr. Raymond D. Adams for giving us access to the neuropathological data on Case 5; and to Dr. John Houghton of the Veterans Administration Hospital in Boston for the clinical and pathological material on Case 6.

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LEGENDS TO PLATES

PLATE XVII

FIG. 1 (*Case I*).—a, Horizontal section through the middle of the cerebral hemispheres, showing the small wedge-shaped infarct in the right post-central gyrus. b, Low power microscopic view. The infarct is represented by a clearly outlined trabeculated cavity. Hæmatoxylin and eosin.

PLATE XVIII

FIG. 2 (*Case II*).—a, Coronal section through the frontal lobes showing the infarct cavity involving the left superior, middle and inferior frontal convolutions. b, Low power microscopic view of a portion of the lesion. Note the extensive cavitation with clearly demarcated walls, connective tissue trabeculæ, and a few remaining islands of cerebral tissue. Hæmatoxylin and eosin.

PLATE XIX

FIG. 3 (*Case III*).—a, Low power microscopic view of a small infarct in the precentral gyrus, showing dense cellularity and marked prominence of blood vessels. Cresyl violet. b, Higher power microscopic view showing large numbers of swollen macrophages and numerous small blood vessels. Cresyl violet.

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PLATE XX

FIG. 4 (*Case IV*).—a, b, Horizontal sections demonstrating the extent of the infarction in the right cerebral hemisphere. Note the numerous fine trabeculæ within the lesion.

PLATE XXI

FIG. 5.—a (*Case I*), High power microscopic view. Giant pyramidal cells of Betz are found in the gyrus appearing on the left in the photograph; the lesion is on the right. The central fissure (of Rolando) lies between. Hæmatoxylin and eosin. b, (*Case IV*), Low power microscopic view of the edge of the lesion. The cavity is clearly outlined, and contains relatively few macrophages. Hæmatoxylin and eosin.

PLATE XXII

FIG. 6 (*Case V*).—Coronal sections showing the extensive involvement of the right superior temporal gyrus.

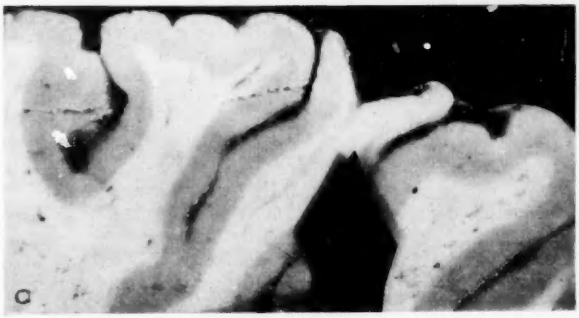
PLATE XXIII

FIG. 7 (*Case VI*).—a, External view of the left hemisphere. The gyri above and below the posterior part of the left Sylvian fissure are atrophic. b, Horizontal section through the superior part of the cerebral hemispheres. At this level the infarct cavity is visible in the left frontal lobe.

PLATE XXIV

FIG. 8 (*Case VI*).—Low power microscopic view of the edge of the infarct. There is extensive cavitation, with blood vessels and connective tissue trabeculæ within the cavity. Hæmatoxylin and eosin. (*Inset*) Higher power microscopic view of the infarct wall demonstrating advanced gliosis. A few macrophages are visible on the right, within the cavity.

PLATE XVII



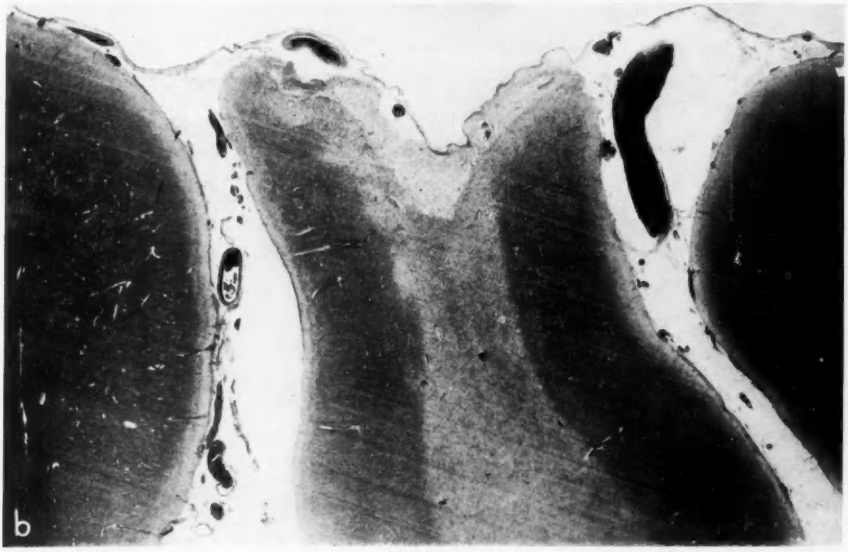


FIG. 1

To illustrate article by Philip R. Dodge, Edward P. Richardson, jr., and Maurice Victor.

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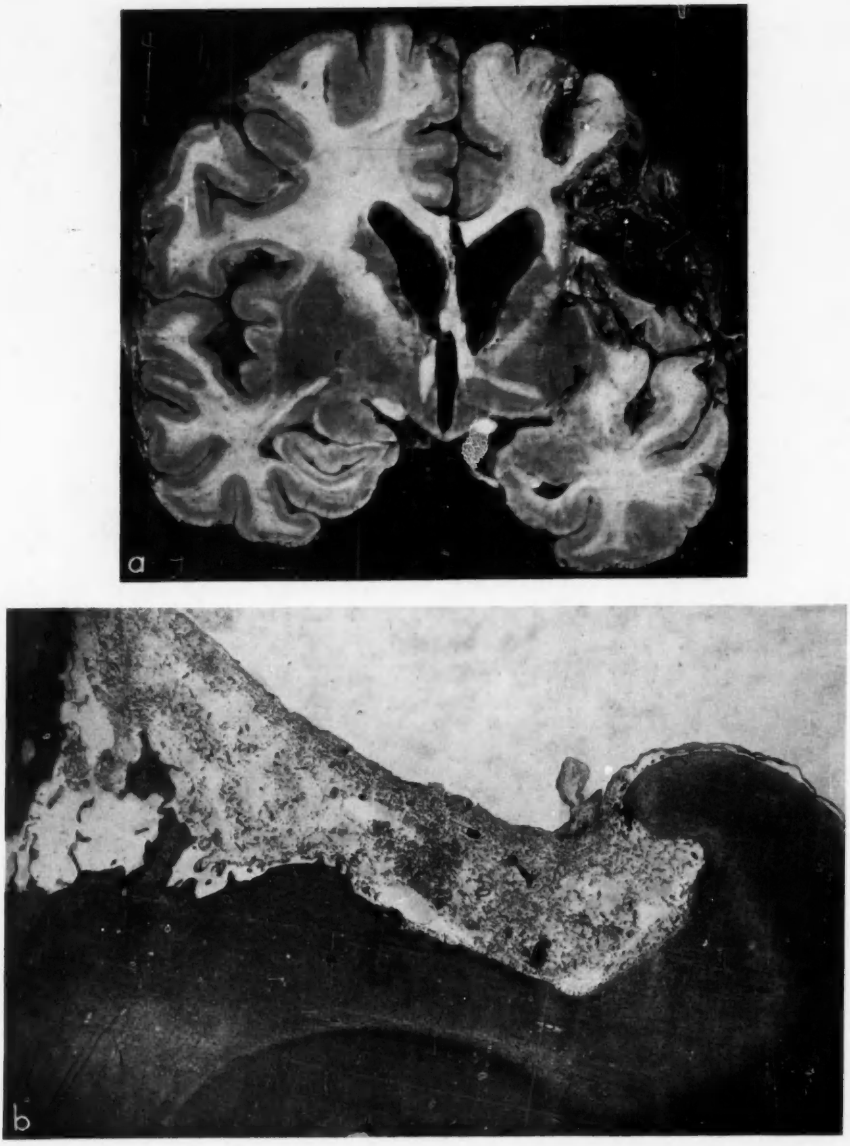

FIG. 2.

To illustrate article by Philip R. Dodge, Edward P. Richardson, jr., and Maurice Victor.

PLATE XIX

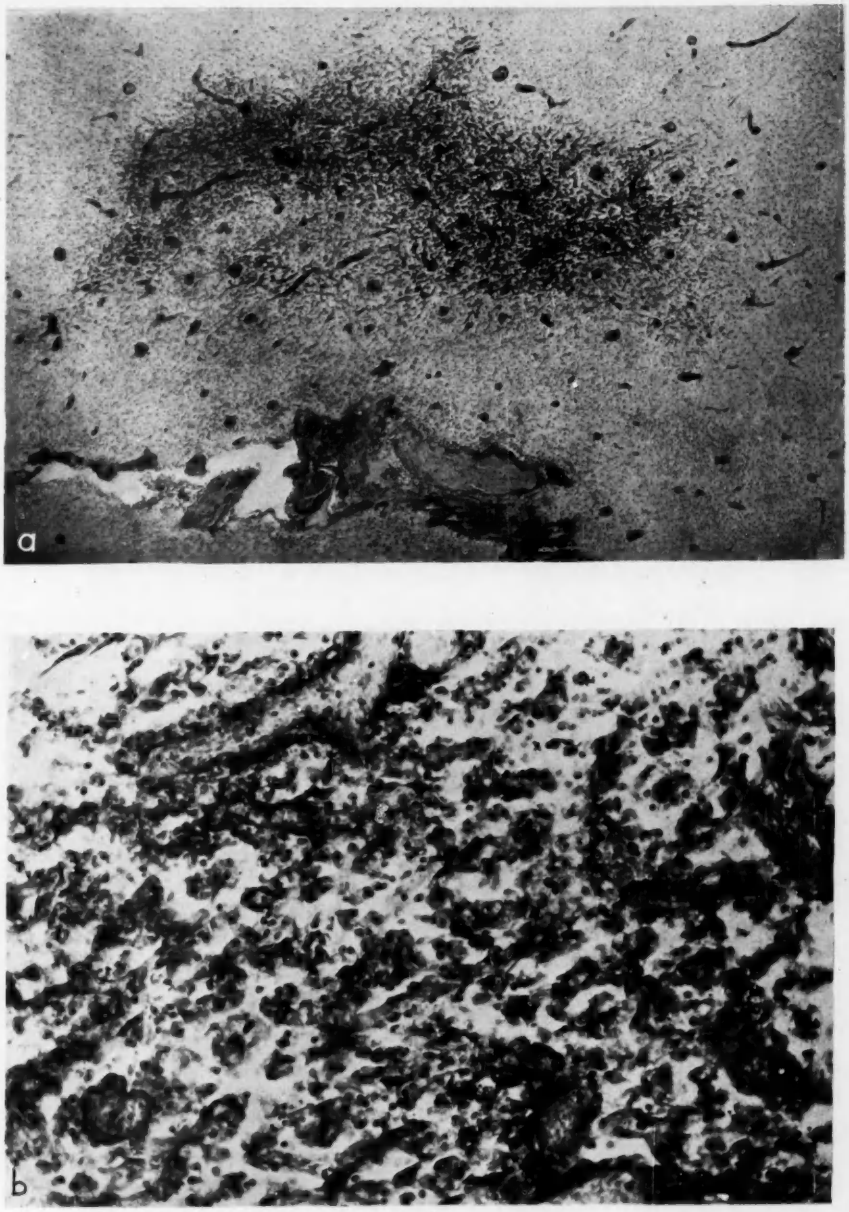

FIG. 3.

To illustrate article by Philip R. Dodge, Edward P. Richardson, jr., and Maurice Victor.

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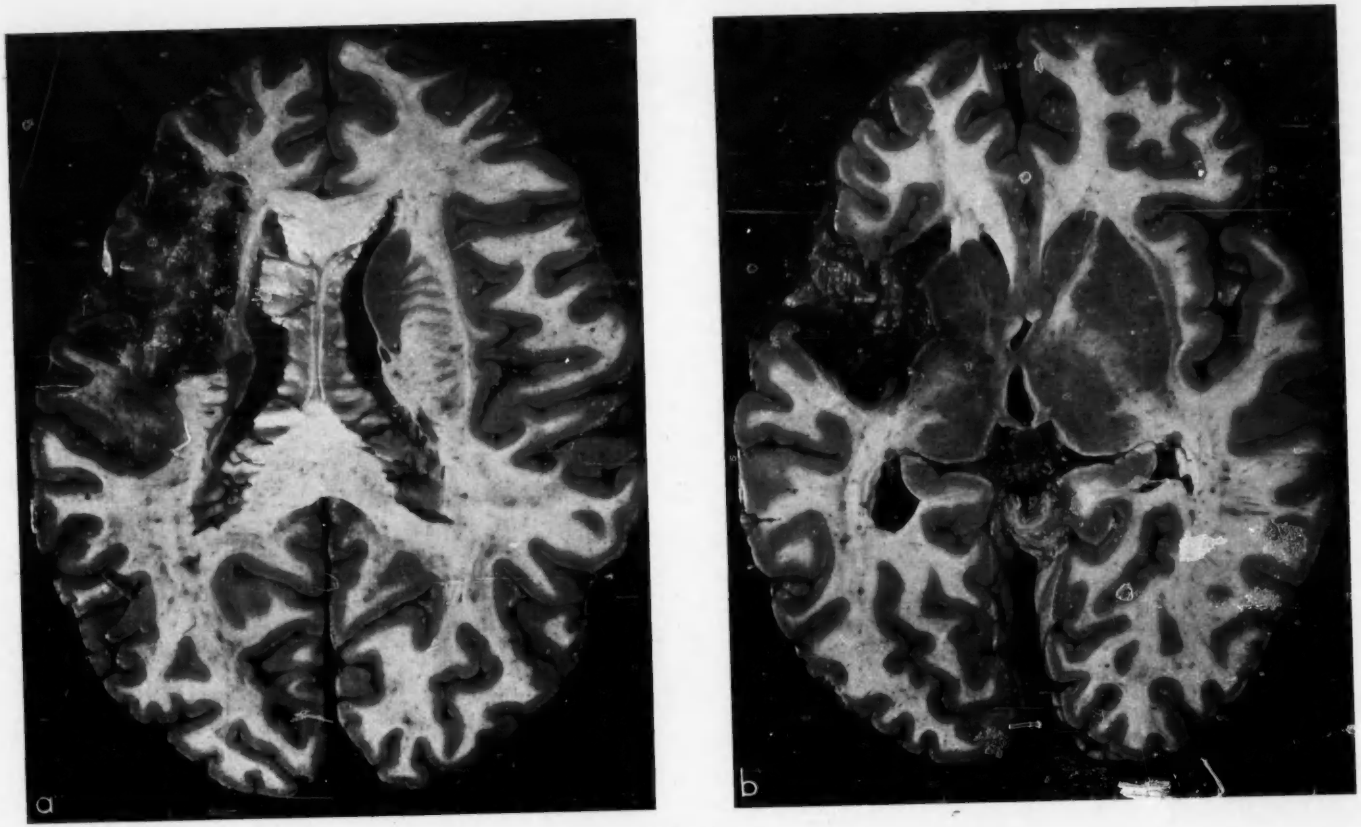

FIG. 4

To illustrate article by Philip R. Dodge, Edward P. Richardson, jr., and Maurice Victor.

PLATE XXI

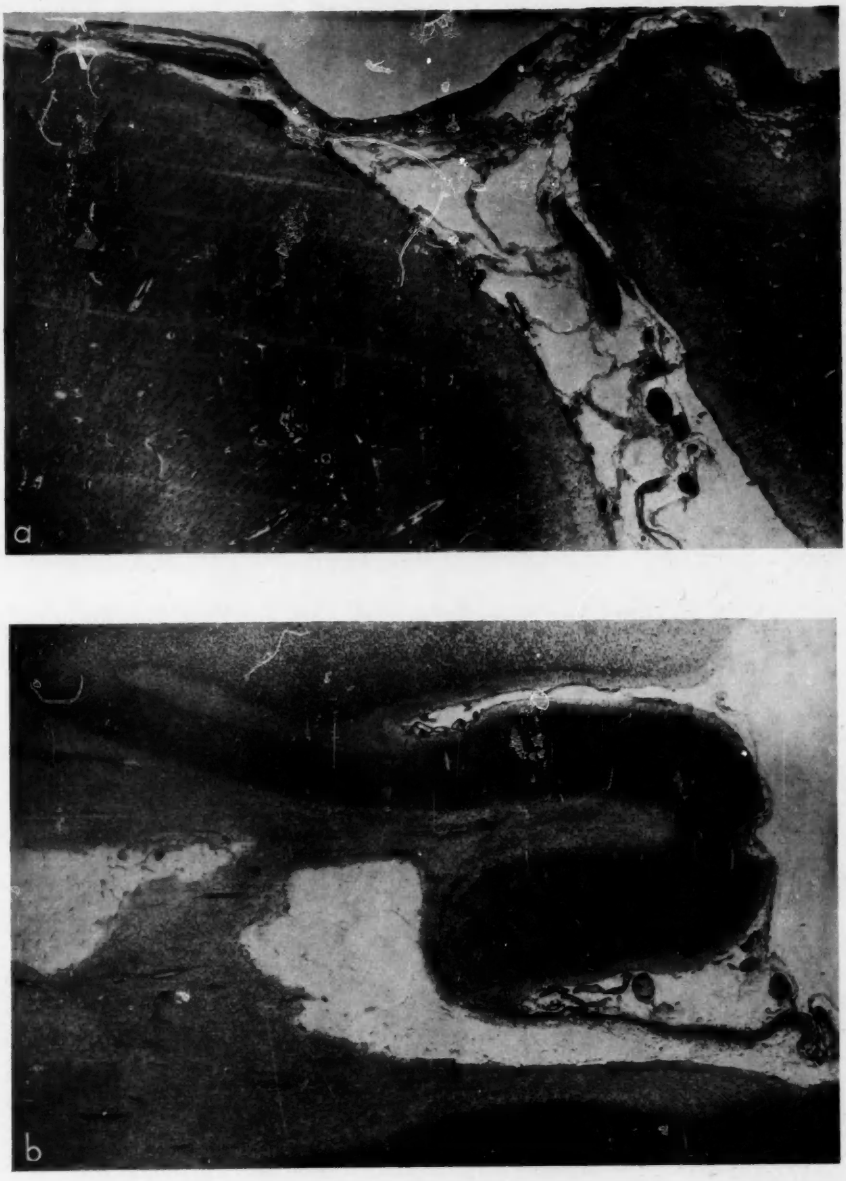

FIG. 5.

To illustrate article by Philip R. Dodge, Edward P. Richardson, jr., and Maurice Victor.

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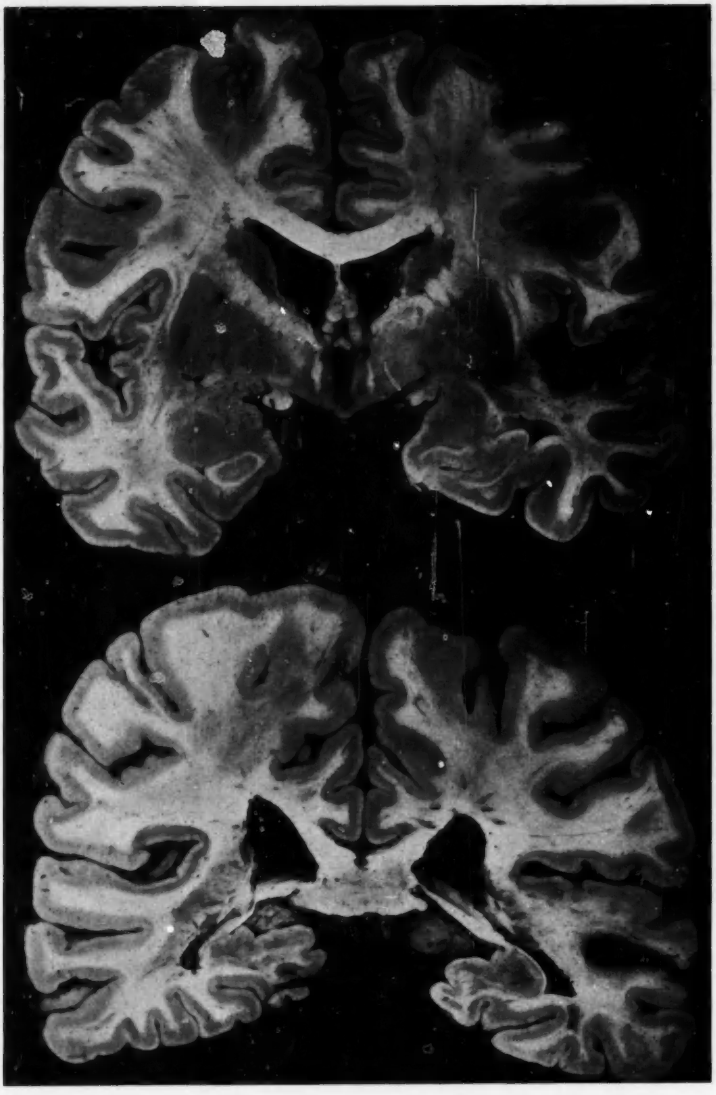

FIG. 6.

To illustrate article by Philip R. Dodge, Edward P. Richardson, jr., and Maurice Victor.

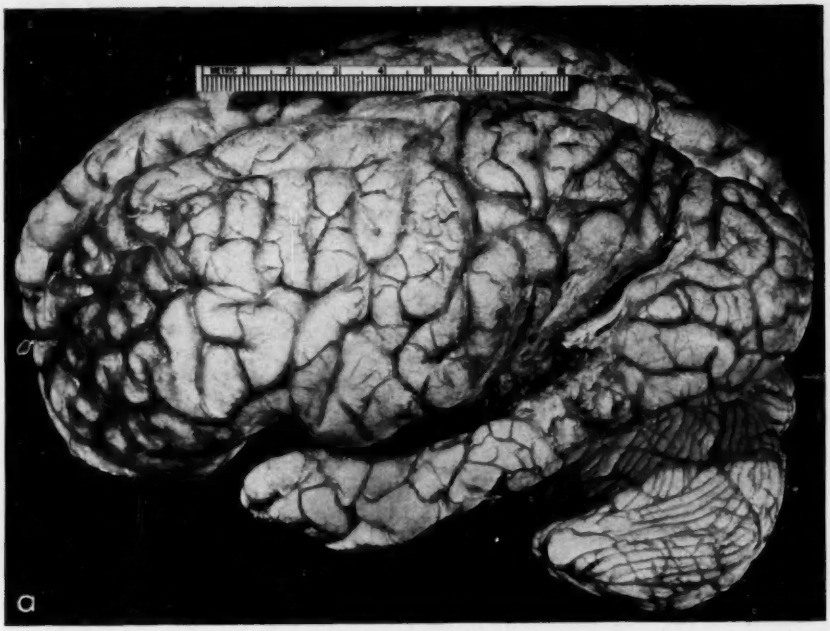

FIG. 7.

To illustrate article by Philip R. Dodge, Edward P. Richardson, jr., and Maurice Victor.

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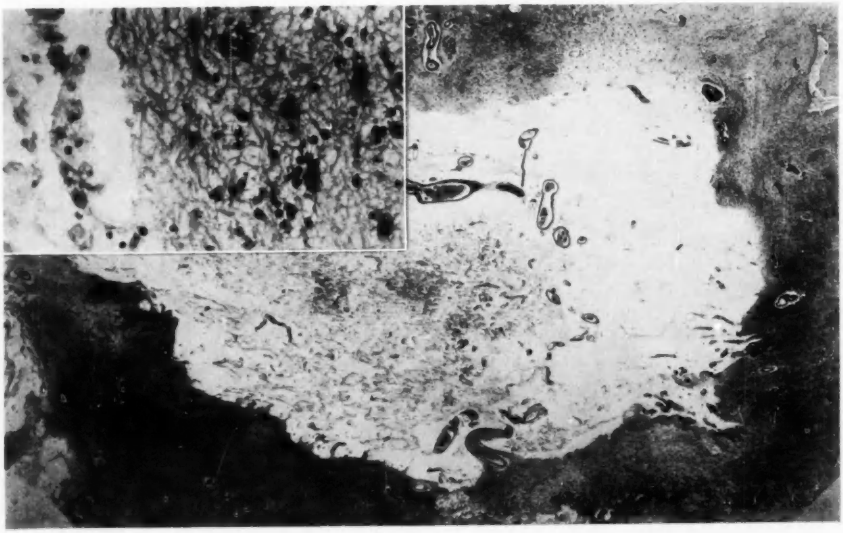

FIG. 8.

To illustrate article by Philip R. Dodge, Edward P. Richardson, jr., and Maurice Victor.

Notices of Recent Publications

Epilepsy and the Functional Anatomy of the Human Brain. By Wilder Penfield and Herbert Jasper. 1954. Pp. 896, 8 colour plates and 314 black and white illustrations. J. and A. Churchill Ltd., London. Price £5 15s.

This book is a sequel to Penfield and Erickson's "Epilepsy and Cerebral Localisation" which has been completely rewritten with a change in the joint authorship. It embodies the practical and theoretical conclusions which have emerged from the work on epilepsy initiated in 1928 by the senior author at the Montreal Neurological Institute where he was joined ten years later by Dr. Jasper.

After a historical introduction there is a chapter devoted to introductory definitions and classifications which sets out the ideas concerning the nature of epilepsy of which the remainder of the book is largely an elaboration. It is stated that "we may consider all epileptic seizures to be the result of a discharge which originates somewhere within the central nervous system and, in that sense, all cases might be considered to be focal. But for practical purposes it is best to apply the term only to those cases in which there is a demonstrable origin in an area of grey matter of one cerebral hemisphere." The idea of idiopathic, meaning self-originating, epilepsy is therefore rejected and cases of epilepsy are divided into two groups (1) those of symptomatic epilepsy, in which a causative lesion or agent has been found, or may be reasonably assumed, and (2) cases of cryptogenic epilepsy, in which no cause has as yet been found. A clinico-anatomical classification recognizes attacks that arise (1) in the cerebral cortex or (2) any subcortical region (centrencephalic) and a third category is (3) one of cerebral seizures—unlocalized. A functional localization in the cerebral cortex is discussed with special reference to the effects of electrical stimulation in man, to the study of which Penfield has made such important contributions. The well-known diagram of the motor sequence in the Rolandic cortex, by which movements are represented in isolated areas, is reproduced, but the text makes it clear that "one representation is not sharply demarcated from adjacent representations."

The series of chapters on motor, sensory, autonomic and psychical seizures contain accounts of numerous varieties of these manifestations of the epileptic discharge, illustrated by case notes and illuminated by reports of the effects of electrical stimulation of the cortex. Then follows a chapter in which the authors develop their idea of the centrencephalic system as the highest level of functional integration in the nervous system and which is regarded as the site of those discharges which cause *petit mal* and *grand mal*. Other topics discussed are the nature of the pathological changes responsible for epileptic attacks and the role of electro-encephalography, electro-corticography and radiography in diagnosis. There is a chapter on surgical therapy, which includes a review of the results of cortical excision, and Dr. Francis McNaughton contributes a chapter on diagnosis and medical treatment.

This comprehensive book is a worthy monument to the valuable contribution to our knowledge of epilepsy which has been made by Penfield and his collaborators at the Montreal Neurological Institute. These workers by their clinical observations, supplemented by electrical stimulation of the brain, have provided us with many new facts and increased our powers to differentiate seizure patterns. It is possible to be

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grateful for these discoveries without necessarily subscribing to all the theoretical conclusions which have been drawn from them. Some of Penfield's most interesting observations have been concerned with the evocation of memories by either local epileptic discharges or electrical stimulation of the temporal cortex. The conclusion that "there are in the temporal cortex innumerable neurone patterns which constitute records of memory," however, does not necessarily follow, for memories may not be "stored" in that area of the brain from which they can be elicited. All that has recently been learned about the role of the central reticular formation in the regulation of consciousness, together with Jasper's experimental production of *petit mal* by stimulation of the interthalamic region, lend support to the view that attacks of loss of consciousness and generalized seizures may well be caused by discharges originating in some central area of the brain. Nevertheless it does not follow that this region must itself be credited with those functions which cannot be efficiently carried out when it is disorganized, nor that its task is, for example, the co-ordination of the nerve impulses concerned in memories into an integrated whole. It is probable indeed that the relationship between the central reticular formation and the cortex is more complex even than the most recent work on cortical-subcortical relationships suggests. Here again we touch the subject upon which, more than any other, new and clear thinking is required, namely, the meaning of cerebral localization.

The surgical approach to the problem of epilepsy employed in Montreal has led to the stress upon its focal origin mentioned at the beginning of this review. All seizures, it is held, would be focal if only we could find the focus. Perhaps as a result of this, the importance of heredity is underestimated; indeed it receives only a brief mention in the book. Yet heredity is important, not only as contributing to the ætiology of "idiopathic epilepsy," but also, as Lennox has shown, as a factor in the causation of epilepsy associated with acquired lesions in some cases. Does heredity operate, however, by causing a focal discharging lesion, or, perhaps, through metabolic abnormalities which predispose to discharge? We do not know. But since many acquired metabolic abnormalities lead to convulsions, and since all drugs which control epilepsy must do so by influencing the metabolism of nerve cells, we should not allow the great contributions which Penfield and his school have made to the elucidation of focal epilepsy to blind us to the importance of research into those aspects of the disorder which come within the province of the physician and the biochemist.

W. R. B.

Contributions to the Study of Cerebral Anoxia. By CYRIL B. COURVILLE. 1953. Pp. 257. San Lucas Press, Los Angeles. Price 6.50 dollars.

This book originated in the important studies which the author made between 1936 and 1941 on the pathology of delayed cerebral death following anæsthesia with nitrous oxide or ether. These impressed him by the variety of the lesions which might result from simple cerebral anoxia. Supported by corroborative evidence from some unusual effects of poisoning by carbon monoxide and cyanide, both in clinical and experimental material, these observations led the author to formulate a theory of "cerebral anoxia" which he now applies to a great variety of the nervous diseases of childhood. This theory is stated as follows:

(1) The primary anoxæmic phase, which may result from a variety of pre-natal, para-natal or post-natal causes, may cause diffuse changes in the cerebral cortex or white matter.

(2) But the anoxæmia may also initiate secondary vascular changes, "presumably through vaso-spasm." These may cause localized softenings or less severe focal regressive changes (microgyria, ulegyria, hemispheral atrophy).

(3) "When these vasomotor or ischæmic disorders are less severe but long continued, there is reason to believe that the central white matter becomes affected and that cystic degeneration (if the process is more severe) or progressive demyelination (a slower degree of change) will be the result."

Some of the author's conclusions may be acceptable, at least in part, to readers who have followed current trends of thought regarding such "congenital" conditions of the brain as status marmoratus, and those found in spastic children and mental defectives. They may, however, disagree with his complete rejection of theories based on arterial or venous thrombosis. Fewer will accept, without more evidence, the theory of para-natal anoxia as the cause of diffuse sclerosis or Schilder's disease, in cases which come on in children who have appeared normal for the first few years of life. The changes which the author has found in the small arteries to the white matter in cases of this kind have not been found by all workers, and the relation of cause and effect here is by no means clear. The enzyme theory of diffuse sclerosis suggested by Hurst and Lumsden is no more acceptable to the author than that of hereditary predisposition. In this, as also in some other parts of the book, the author's insistence on the theory of cerebral anoxia as the sufficient cause, and the only cause supported by factual evidence, savours of special pleading. But if he appears to have omitted some evidence pointing in other directions, he has certainly collected an impressive array of evidence in favour of his own theory.

The wide survey of the literature, covering nearly five hundred references, and the many interesting case-histories given in Chapter II, give special value to this book, which deserves serious study, especially by those interested in congenital disorders of the nervous system.

J. G. G.

Prefrontal Leucotomy and Related Operations. Anatomical Aspects of Success and Failure. By ALFRED MEYER and ELIZABETH BECK. 1954. No. of Illus. 20. Pp. 60. Oliver and Boyd Ltd., Edinburgh. Price 10s. 6d.

The authors provide a most painstaking and careful review of the anatomical findings in one hundred and two brains subjected to leucotomy at a minimum period of seven months before death. The object has been to compare the extent of the lesion in the frontal lobe and basal ganglia with the improvement in the clinical state and the degree of personality change induced by operation.

The assessment does not, of course, give a true picture of the clinical result of psychosurgery, for the material is not widely representative. As the authors point out, post-mortem material is more easily obtained in cases of failure or but partial success, when the individuals have remained inmates of mental hospitals. Sufficient material from the more successful cases has been obtained to enable the authors to show that the amount of anatomical isolation of the frontal lobe is definitely greater in cases improved by operation than in those in whom it has failed: they have also shown that quantitative adequacy is as necessary in open as in blind operation. Evidence is brought to suggest that the anatomical lesion in the mid-central, orbital and cingulate regions is more likely to bring improvement in the mental state than one involving the dorsal and dorso-lateral white matter: lesions involving these latter areas would appear to be productive of greater personality change. The authors thus point to some regional localization combined with the need for a sufficient quantitative lesion for the achievement of good therapeutic results.

The monograph is admirably produced and clearly illustrated with tables, diagrams and photographs. It is a most important contribution to the anatomical

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aspects of neurosurgical intervention in the treatment of mental illness and should prove of the greatest interest to all workers in this field of medicine.

W. McK.

Descartes' Philosophical Writings. Collected and Translated by NORMAN KEMP SMITH. 1952. London: Macmillan & Co. Ltd. Pp. 316. Price 25s.

New Studies in the Philosophy of Descartes. By NORMAN KEMP SMITH. 1952. London: Macmillan & Co. Ltd. Pp. 369. Price 25s.

It is doubtful if any philosopher has influenced neurology as much as René Descartes. His statement of the problem of the body-mind relationship has profoundly affected all theoretical and practical workers in this field, and continues to do so, although there is some evidence that his influence is now on the wane. These two volumes show how much that we nowadays take for granted in our neurological thinking is either attributable to Descartes or was already recognized by him. Thus, he appreciated the nature of reflex action in animals and in man: he thought in terms of brain patterns which were a product of motion and configuration, and he regarded such patterns as playing an equally important part in sensation and memory. He was aware that sensations enter consciousness only if their afferent impulses reach a certain part of the brain, and he knew that excitation of a sensory pathway from the foot to the brain might cause the subject to believe that the foot itself was being stimulated. His postulation of the pineal gland as the site of the soul was derived from the fact that, although the eyes form two images of any object we see and their nervous pathways are everywhere reduplicated, we, nevertheless, see one object and not two. There must, therefore, he thought be some single point in the nervous system at which a fusion of images occurs.

In the "Philosophical Writings" Mr. Kemp Smith has collected and translated all Descartes' important philosophical work, his letters on the mind-body problem and a section from "Passions of the Soul." His "New Studies" are essays on Descartes' thought, whose tenour is shown in the subtitle, "Descartes as Pioneer." W. R. B.

2ND INTERNATIONAL CONGRESS OF NEUROPATHOLOGY

The 2nd International Congress of Neuropathology has been arranged for September 12–17, 1955, in London.

Offers of contributions should be sent to Dr. W. H. McMenemey, Maida Vale Hospital for Nervous Diseases, London, W.9, from whom further particulars may be obtained.

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